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1. Moyer, J. H., et al.: Am. J. M. Sc. *225*:379 (April) 1953.
2. Mills, L. C., and Moyer, J. H.: A.M.A. Arch. Int. Med. *90*:587 (Nov.) 1952.
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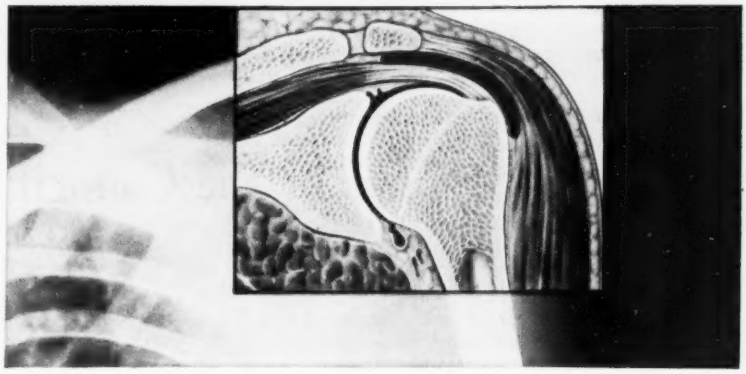

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1. J. A. M. A. 151 (1953):5, p. 366

2. Postgraduate Med. J. 10(1951), p. 317

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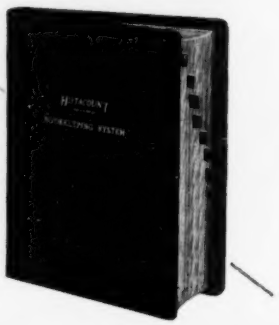

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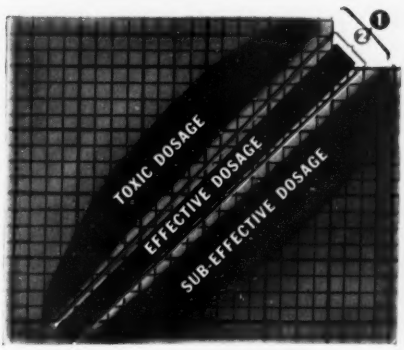

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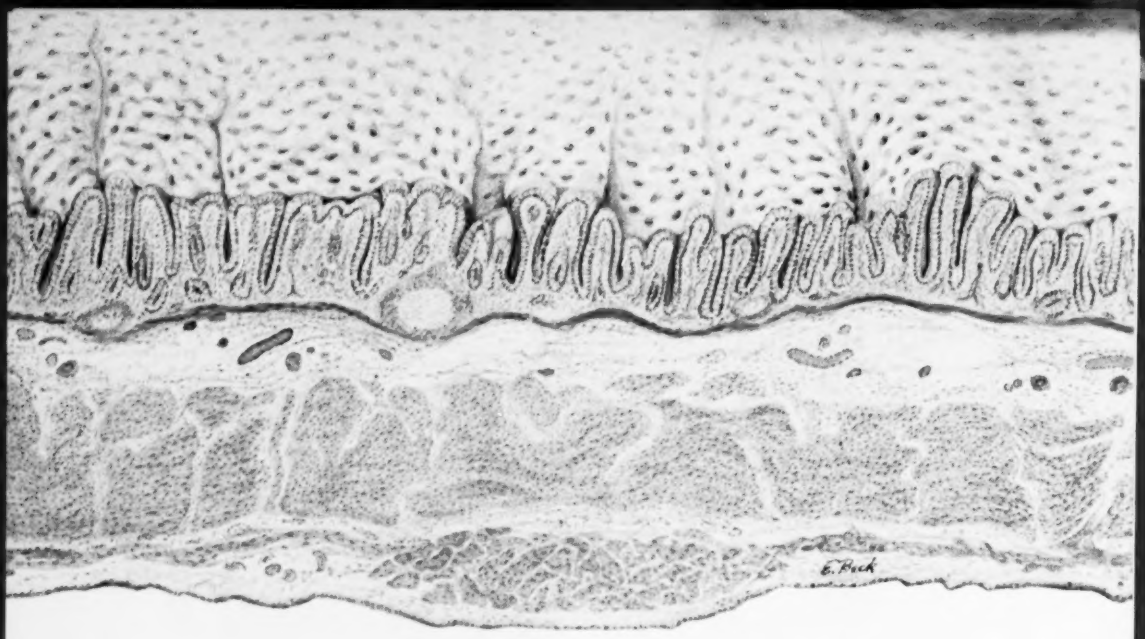

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VOLUME 92 NOVEMBER 1953 NUMBER 5

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Editorials

THERAPY OF ASCITES IN PATIENTS WITH CIRRHOSIS OF THE LIVER

AT THE turn of the century it was generally assumed that high pressure in the portal system was the cause of the ascites which occurred with cirrhosis of the liver; the doctor hoped that development of collateral circulation would lead to disappearance of the fluid, and much attention was paid to the anatomy of possible channels. Herrick [1] tackled the problem experimentally and concluded that "the communication of the arterial pressure to the portal pressure is an important factor in an explantion of the increased portal pressure in portal cirrhosis" and that compression of the venous radicles by fibrous tissue was perhaps of less consequences. However, even fifty years ago, those giving careful thought to the subject were not sure that portal obstruction was the entire answer to the problem of "cirrhotic" ascites. In his classical monograph, Rolleston,[2] for example, raised the question of whether poisons developing during the course of the disease might not damage the vessels so as to allow transudation, to some extent anticipating modern views. He also thought that ascites might be due to concomitant perihepatitis or to cardiac failure and possibly confused true cirrhosis with constrictive pericarditis.

Many new ideas about the causation of ascites have sprung up in the last decade with the development of modern knowledge of colloid osmotic pressure and of electrolyte and renal physiology. In 1945, for example, Hoagland and his associates [3] pointed out that ascites might wax or wane without significant alteration in the level of serum albumin (see below). They found however that the urine of patients with ascites when injected into hydrated rats delayed the excretion of urine, and they felt that an abnormally intense antidiuretic influence played a part in the causation of ascites. The exact nature of the mechanism was not clear. Meanwhile the question of whether accumulation of peritoneal fluid was promoted by low plasma albumin again came under lively dispute. The problem was well sumarized by Patek and his group, [4] who concluded that ascites was not solely determined by the level

1. Herrick, F. C.: An Experimental Study Into the Cause of the Increased Portal Pressure in Portal Cirrhosis, J. Exper. Med. **9**:93, 1907.

2. Rolleston, H. D.: Diseases of the Liver, Gall-Bladder, and Bile-Ducts, London, Macmillan & Co., Ltd., 1912, p. 243 and following.

3. Ralli, E. P.; Robson, J. S.; Clarke, D., and Hoagland, C. L.: Factors Influencing Ascites in Patients with Cirrhosis of the Liver, J. Clin. Invest. **24**:316, 1945.

4. Patek, A. J., Jr.; Mankin, H.; Colcher, H.; Lowell, A., and Earle, D. P., Jr.: The Effects of Intravenous Injection of Concentrated Human Serum Albumin Upon Blood Plasma, Ascites and Renal Functions in 3 Patients with Cirrhosis of the Liver, J. Clin. Invest. **27**:135, 1948.

of plasma colloidal osmotic pressure. They considered the participation of other factors such as changes in permeability of the portal vascular bed and alterations of salt and water metabolism. Others, however, as for example Kunkel and his associates,[5] found serum albumin infusions useful, and in their series 14 out of 15 patients lost their ascites following such therapy. From 4 to 80 units of albumin were necessary to produce a satisfactory effect in various cases. These findings have apparently been confirmed by some, although variously judged by others. Goodyear [6] and his colleagues emphasized the role of salt retention in promoting ascites in cirrhotic patients. They concluded from observations on the excretion of infused sodium chloride that there exists in cirrhotic patients with edema or ascites a specific impairment of the renal mechanism for the excretion of sodium.

Others have abundantly confirmed these findings,[7] although the ultimate nature of the disturbance has not yet been established. A recent summary is given by Eisenmenger.[8] He found that formation of ascites was arrested in most of his patients by a diet containing only about 17 mEq. a day of sodium. Kark [9] in an interesting paper emphasizes further the importance of diseased and abnormally permeable vascular endothelium in the development of ascites and believes that disappearance of fluid after high protein diets is due in part to the building of a healthy "endothelial protoplasmic barrier" against leakage of serum into the peritoneum.

It seems, then, that a number of factors may play a part in the formation of ascites, to wit:

Portal hypertension
Abnormally permeable vascular endothelium
Antidiuretic Influences
Inability to excrete sodium
Low colloidal osmotic pressure of plasma

Some of these may be interrelated, and the exact role of certain endocrine glands, such as the adrenal, is not yet entirely clear. It does appear, however, that not all of these influences are equally important in every case. As regards the matter of sodium excretion, for example, great differences have been found to exist. Thus, there are patients who fail to reaccumulate ascites or do so very slowly on a sodium-free diet whereas there are others who despite maximal salt restriction rapidly collect fluid in the peritoneum.[10] Doctors are now learning to their cost that arbitrary restriction of sodium in patients who continue to form ascites, especially if paracentesis is done, may provoke serious or even fatal effects of salt depletion. Coinci-

5. Kunkel, H. G.; Labby, D. H.; Ahrens, E. H.; Shank, R. C., and Hoagland, C. L.: The Use of Concentrated Human Serum Albumin in the Treatment of Cirrhosis of the Liver, J. Clin. Invest. **27**:305, 1948.

6. Goodyer, A. V. N.; Relman, A. S.; Lawrason, F. D., and Epstein, F. H.: Salt Retention in Cirrhosis of the Liver, J. Clin. Invest. **29**:973, 1950.

7. Ricketts, W. E.; Eichelberger, L., and Keisner, J. B.: Observations on the Alterations in Electrolytes and Fluid Balance in Patients with Cirrhosis of the Liver With and Without Ascites, J. Clin. Invest. **30**:1157, 1951.

8. Eisenmenger, W. J.: Role of Sodium in the Formation and Control of Ascites in Patients with Cirrhosis, Ann. Int. Med. **37**:261, 1952.

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10. Lowe, C. R., and Overy, D. C.: An Evaluation of Rigid Dietary Sodium Restriction in the Management of Ascites in Cirrhosis of the Liver, Ann. Int. Med. **34**:1396, 1951.

dent drastic disturbances of electrolytes other than sodium may also develop.[11] We have seen a cirrhotic patient who, after an abdominal tap, while on rigid salt restriction, suddenly developed complete flaccid paralysis of all four extremities. Potassium disturbance was suspected, and the serum potassium was found to be 10 mEq. per Liter. On intravenous infusion of sodium chloride there was rapid recovery, and the patient subsequently did well as long as salt was not restricted. There are now a number of reports of similar occurrences in the literature. Nelson, Rosenbaum, and Strauss,[12] for example, describe two well-studied cases. Weakness, going on to serious prostration, nausea, low serum sodium, and hyperkalemia, followed tapping when these patients were on a salt-free diet. Lowe and Overy [10] report a fatal case.

The moral of all this is that it is unsafe invariably to base one's therapy of ascites on any one measure. One should know that, even though it is often useful, not every patient will respond to salt restriction with failure to reaccumulate fluid and that grave danger exists if a low-salt regimen is pursued in the face of such reaccumulation. Every cirrhotic patient is, to be sure, entitled to one carefully controlled trial to find out what salt restriction will do. After a preliminary tap salt should be withdrawn from the diet. If ascites fails to collect, well and good, but if fluid does return with any speed salt restriction should be abandoned and dependence placed on tapping, rest and upbuilding with proper diet and vitamins if the low salt syndrome is to be avoided.

ARTHUR L. BLOOMFIELD, M.D.

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11. Hilton, J. G.: Effects of Mercurial Diuresis in Patients with Ascites Due to Cirrhosis, Am. J. Med. **12**:311, 1952.

12. Nelson, W. P., III; Rosenbaum, J. D., and Strauss, M. B.: Hyponatremia in Hepatic Cirrhosis Following Paracentesis, J. Clin. Inves. **30**:738, 1951.

DIFFUSE INTERSTITIAL FIBROSIS OF LUNGS

A Form of Diffuse Interstitial Angiosis and Reticulosis of the Lungs

ALFRED GOLDEN, M.D.
AND
THEODORE T. BRONK, M.D.
BUFFALO

DIFFUSE interstitial fibrosis of the lungs was the subject of editorial comment in *The Journal of the American Medical Association*, Jan. 17, 1953.[1] This summarized the reports of the relatively small number of cases that have appeared in the medical literature since attention was called to this entity by Hamman and Rich.[2]

It is the purpose of this presentation to summarize the salient clinical features from the published reports and from our current experience with three cases and to present the pathological findings in our cases. We found the phase microscope [3] and the McManus-Schiff reaction particularly useful in combination with observations made by means of the Masson trichrome stain, the Wilder reticulum method, and the Weigert elastic tissue stain as well as hematoxylin and eosin stained sections.

Pulmonary lesions in these cases were compared with those seen in acute interstitial pneumonia or primary atypical pneumonia; in pulmonary fibroses, other than the diffuse interstitial type; in chronic passive congestion of the lungs secondary to mitral valvular disease, and in diffuse pulmonary fibrosis after x-ray exposure.

REPORT OF CASES

CASE 1.—*Clinical Abstract.*—A 50-year-old white man was admitted to this hospital in extremis and lived for only one and one-half days. The family stated that the patient had been dyspneic on exertion for "a long time" but had remained fairly comfortable until one week prior to his hospital admission, when he caught a cold. Dyspnea promptly increased to orthopnea, and the cough became productive of large amounts of dark fluid but no frank blood. The temperature at the time of admission, was 100 F., the pulse rate was 120 per minute, and the respiratory rate was 34 per minute. Physical examination revealed numerous coarse bubbling rhonchi and rales throughout both lung fields. The red blood cell count was 5,800,000 per cubic millimeter, and there were 15.4 gm. of hemoglobin per 100 cc. The patient was placed in an oxygen tent and was given meperidine (Demerol), aminophylline, and mersalyl (Salyrgan) intravenously. The patient's cyanosis remained, and dyspnea was unrelieved. His pulse became irregular; he lapsed into coma and died.

From the Laboratory Service, Buffalo Veterans Administration Hospital (University of Buffalo School of Medicine).

Read before the Section on Pathology and Physiology at the 102nd Annual Session of the American Medical Association, New York, June 3, 1953.

1. Acute Diffuse Interstitial Fibrosis of the Lungs, editorial, J. A. M. A. **151**:215 (Jan. 17) 1953.

2. Hamman, L., and Rich, A. R.: Acute Diffuse Interstitial Fibrosis of the Lungs, Bull. Johns Hopkins Hosp. **74**:177-212 (March) 1944.

3. The American Optical Company instrument using the dark medium contrast 4 mm. objective and the "C" condenser proved to be the most useful combination for this study.

Postmortem Findings.—The significant findings were limited to the lungs and the heart. Grossly, the lungs were lightly anthracotic, fleshy, and had markedly reduced crepitus and no gross evidence of emphysema. The right lung weighed 750 gm. and the left lung, 525 gm. On each side, the cut surfaces were moderately red, fairly dry, and, particularly in oblique illumination, showed a coarsening of the usual spongy architecture. There was no evidence of consolidation. The tracheobronchial tree had hyperemic mucosal surfaces throughout and contained a moderate amount of mucopurulent fluid. The tracheobronchial lymph nodes were not remarkable.

Microscopically, there was widespread, almost universal, hypertrophy of alveolar walls but they were of variable thickness. Under the phase microscope and by means of the McManus-Schiff reaction the thickness of the alveolar wall was clearly seen to be on the basis of capillary proliferation. Such walls showed layering of such capillaries from two to six and even more. The cross-section diameters of such capillaries were increased to accommodate two to six red blood cells within their lumens. While the alveolar walls varied moderately in their degree of hypertrophy, reticulin fiber hyperplasia within the thickened walls was universal and was in direct proportion to the degree of such hypertrophy. These fibers tended to course along the alveolar walls in multiple layers with many branchings and tended to surround the hyperplastic capillaries. Collagenous increase, however, was by no means directly proportional to alveolar wall thickness. In most zones there was no appreciable increase in collagenous fibers. Where the degree of interstitial collagenous deposition was greatest, the number of proliferated capillaries was reduced but still increased over the normal. The elastic tissue components were not altered appreciably. Peribronchial, perivascular, and interlobular septal tissues showed no significant changes from the normal. Occasionally, bronchial lumens, particularly in the smaller branches, contained small numbers of leucocytes.

The 500 gm., hypertrophied heart had a markedly thickened right ventricular wall, which measured up to 10 mm., and a markedly dilated right atrium. There were no valvular abnormalities.

Case 2.—*Clinical Abstract.*—A 50-year-old white man had two hospital admissions a few months apart, with an initial diagnosis of chronic pulmonary fibrosis with cor pulmonale and congestive failure. Tuberculosis was suspected clinically, but no proof was obtained. The patient had been a grinder for two years, many years ago. Four days prior to his last hospital admission dyspnea and cough developed. The latter became progressively worse, and the patient's distress was out of proportion to the physical findings. Cyanosis and an appearance of acute illness were associated with a pulse rate of 130 per minute, with many rales in both lung fields, and with a pulmonic second sound greater than the aortic second. The digits of both hands and feet showed clubbing. The patient responded poorly to oxygen therapy. He died shortly after his second admission.

Postmortem Findings.—Both lungs showed markedly reduced crepitus and increased firmness and were of markedly increased weight. The left weighed 1,700 gm. and the right, 1,900 gm. As seen by repeated cross section through both lungs, the lesion had resulted in the transformation of lung substance into a diffusely coarsely honeycombed structure without visible nodularity or consolidation. The lung tissue itself varied from pale pink to translucent gray and, in its most densely fibrotic areas, had a definitely silvery sheen. The septa in the interlobular zones were outlined by such glistening, gray fibrosis, and through the pleura the lung assumed a mammilated configuration. Anthracosis in both lungs was mild. Tracheobronchial lymph nodes were not remarkable. The tracheobronchial tree contained a small amount of mucoid secretion.

Microscopically, many sections of the lungs showed findings essentially similar to those described in Case 1. However, while collagenous increase was minimal in Case 1, it was appreciable and fairly widespread in this case. Fibers staining positively by the Masson technique for collagen contributed materially to the hypertrophy of some alveolar walls. Some of the larger bronchi contained a moderate amount of purulent secretion within their lumens and mild round cell reactions in the peribronchial tissues. Here and there, alveolar lining cells were prominent and formed poorly defined layers and, by fusion, occasional giant cells with few nuclei. Minute pools of coagulable fluid were scattered in alveolar lumens but, for the most part, as in Case 1, the air spaces were free except for the presence of moderate numbers of anthracotic stippled phagocytes. Isolated clusters of round cells and few eosinophiles were present interstitially, admixed with the elements that comprised alveolar wall hypertrophy, but they contributed little to such thickenings. An incidental finding in over 50 lung sections taken from different parts of

the lung consisted of two small tuberculous granulomas, which were interpreted as having played no part in the evolution of alveolar wall hypertrophy of this diffuse type.

CASE 3.—*Clinical Abstract.*—A 63-year-old white man whose illness goes back "several years" had a hospital record of cough for at least two years and shortness of breath for at least three months. At the time of his last hospitalization he was able to walk no more than a block or two without becoming very short of breath but there was no chest pain. He had had no exposure to noxious inhalants. On admission he was afebrile. His pulse rate was 84 per minute, respirations were 18 per minute, and physical findings were limited to the presence of rales in both lung fields. Repeated sputum examinations were negative for tubercle bacilli. The histoplasmin and coccidioidin skin tests were negative. A second strength purified protein derivative test dose was read as 2+. Bronchoscopy showed no abnormalities. Terminally, the patient showed low grade temperature increases to between 100 and 101 F. which responded to antibiotics but recurred as soon as the drugs were stopped. Episodes of severe coughing and choking became more frequent and were accompanied by hyperventilation, cyanosis, and the production of a small amount of bloody sputum. Dullness appeared in the right lower lung coincident with a temperature rise to 104 F. The pulse rate rose to 150 per minute, and respirations increased to about 50 per minute. The patient improved slightly in an oxygen tent, but several hours later Cheyne-Stokes respiration developed and he died.

Postmortem Findings.—The significant findings were limited to the lungs. As in the two cases described above, the lungs were firm, moderately anthracotic, and heavy. The left lung weighed 825 gm., the right 900 gm. The pleural surfaces were smooth and showed definite subpleural accentuation of the lobular markings, producing a cobblestone surface. On section, there was fairly uniform replacement of lung substance by firm, almost meaty, medium red coarse sponginess. The greatest portion of the lung surfaces showed this transformation, while along the pleural margins there were irregular radiating patches of silvery fibrosis streaked with anthracosis. These subpleural layers varied from a few millimeters to 0.5 cm. in thickness. The tracheobronchial tree was not remarkable.

Many sections were taken for microscopic examination. Alveolar wall hypertrophy was practically universal and differed from those instances described above in that there was variation from areas in which there was barely perceptible alveolar wall hypertrophy to others in which the alveolar septa were enormously increased in width. The reticulum meshwork in such areas was heavier than in either of the cases described above. Alveoli lined by a metaplastic columnar epithelium, sometimes squamous, was confined to those portions of the lungs in which there were the broadest zones of fibrosis with isolation of alveoli. Similarly, the densest depositions of collagen were present in such broad zones and radiated as fibers of variable thickness into adjacent alveolar walls. Phase microscopy, and to a lesser extent the McManus-Schiff reaction, showed that capillary proliferation was abundant even in these most densely collagenous zones. In this case there was frank, focal, apparently terminal bronchopneumonia. In this case only, was there any appreciable degree of arterioclerosis with narrowing of the medium-sized blood vessels. This was not necessarily confined to the zones of densest fibrosis.

SUMMARY OF CASES

In none of the three cases is interstitial inflammatory exudate of any kind a prominent feature. All three patients were initially afebrile, had symptoms of at least weeks' to months' duration, and complained of dyspnea and cough with expectoration, and cyanosis developed in all. One had curvature of the nails of the hands and feet. Terminal temperature rises and increased pulse and respiratory rates preceded death in all cases. Grossly, the lungs were of markedly increased weight, with coarsening of the lobular markings as seen under the pleural surfaces. On cut section they all presented the appearance of firmness associated with fairly uniform diffuse and bilateral coarsening of the usual spongy lung tissue (Fig. 1). Two of the three patients had definite cor pulmonale. One had a mild degree of polycythemia.

It is noteworthy that in case 3 there was the greatest degree of interstitial collagenization of alveolar walls but there was no cor pulmonale. In the other two cases

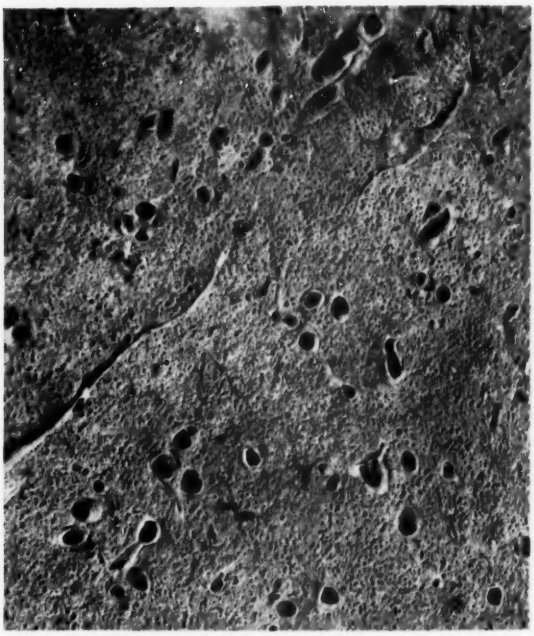

Fig. 1.—Close-up of gross lung specimen from Case 3, showing diffuse coarsening of the lung architecture. Actual size.

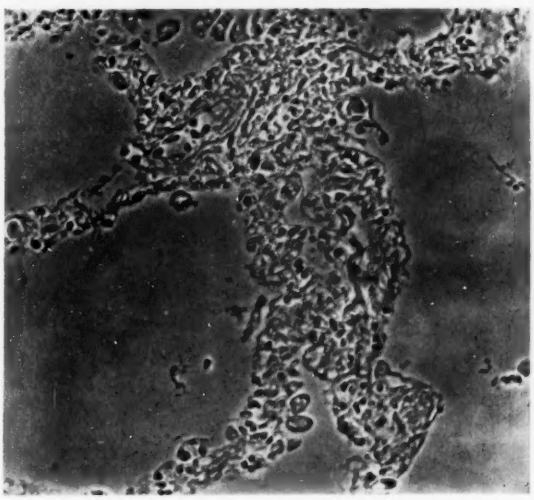

Fig. 2.—High-power phase microscope view of alveolar wall hypertrophy, showing characteristic great content of proliferated capillaries and fine fibrillar meshwork; from Case 2; × 300.

diffuse interstitial wall hypertrophy of the lungs was, as in Case 1, mainly on the basis of capillary proliferation of an extreme degree (Fig. 2), with hyperplasia of reticulum fibers as well (Fig. 3). In Case 2, the addition of small amounts of collagenous stroma was superimposed on this type of reticuloangiosis. The latter more than anything else accounted for the degree of alveolar septal hypertrophy. Metaplasia of alveolar lining cells was striking only in Case 3. Focal edema, alveolar hemorrhage, and focal bronchopneumonia were apparently terminal changes superimposed on the underlying lesion.

CLINICAL CONSIDERATIONS

The Table summarizes the clinical and laboratory data that appear common in these pulmonary lesions.[4] The disease is one of adult life. Males and females, Negro and white are affected.

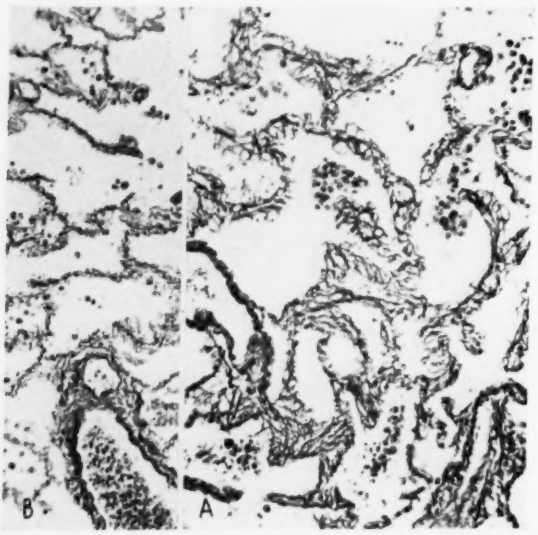

Fig. 3.—*A*, section from Case 2, showing the profusion of reticulin fibers in hypertrophied alveolar walls. *B*, a view of a normal lung for comparison. The magnification is the same. Wilder stain; × 100.

4. (*a*) Eder, H.; Hawn, C. V., and Thorn, G. W.: Report of a Case of Acute Interstitial Fibrosis of the Lungs, Bull. Johns Hopkins Hosp. **76**:163-171 (April) 1945. (*b*) Hamman and Rich.[2] (*c*) Beams, A. J., and Harmos, O.: Diffuse Progressive Interstitial Fibrosis of the Lungs, Am. J. Med. **7**:425-430 (Sept.) 1949. (*d*) Golden, A., and Tullis, I. F., Jr.: Diffuse Interstitial Fibrosis of the Lungs, Mil. Surgeon **105**:130-137 (Aug.) 1949. (*e*) Callahan, W. P., Jr.; Sutherland, J. C.; Fulton, J. K., and Kline, J. R.: Acute Diffuse Interstitial Fibrosis of the Lungs, A. M. A. Arch. Int. Med. **90**:468-482 (Oct.) 1952. (*f*) Rubin, E. H.; Kahn, B. S., and Pecker, D.: Diffuse Interstitial Fibrosis of the Lungs, Ann. Int. Med. **36**:827-844 (March) 1952. (*g*) Golden and Bronk, the three cases in the present paper. (*h*) Spain, D. M.: Patterns of Pulmonary Fibrosis as Related to Pulmonary Function, Ann. Int. Med. **33**:1150-1163 (Nov.) 1950. (*i*) Katz, H. L., and Auerbach, O.: Diffuse Interstitial Fibrosis of the Lungs: (Report of a Case with Unusual Features), Dis. Chest **20**:366-377 (Oct.) 1951. (*j*) Heppleston, A. G.: Chronic Diffuse Interstitial Fibrosis of the Lungs, Thorax **6**:426-432 (Dec.) 1951. (*k*) Peabody, H. D., Jr.; Moersch, H. J., and Edwards, J. E.: Clinically Indeterminate Pulmonary Fibrosis: A Pathologic Study, J. Thoracic Surg. **21**:519-531 (May) 1951.

In the original report of Hamman and Rich [2] this entity was called acute diffuse interstitial fibrosis of the lungs. The duration of symptoms in published reports is variable. Our experience indicates that the onset of symptoms is vague. We suspect that what has been considered acute in this disease is, in reality, the terminal state. Our exprience indicates that the duration of symptoms is long and that the disease develops progressively.

The clinical triad of dyspnea, cyanosis, and cough, while fairly constant in all cases, shows variation in time of onset, severity, and persistence. Some reports describe wide varieties and large numbers of altered breath sounds, while others state negative findings. Temperature elevations, increased respiratory rates, and

Summary of Salient Clinical Features in Cases of Diffuse Interstitial Fibrosis of Lungs

	Age	Sex	Race	RBC, Million/ Cu. Mm.	Hb, Gm./ 100 Cc.	Rt. Ventricle Wall		Duration of Symptoms
						Thickness *	Mm.	
Eder, Hawn, & Thorn [4a]	47	M	W	4.5	16.5	H	7	.....
Hamman & Rich [4b]	41	M	N	5.98	....	H	...	3 mo. or more
	21	F	N	5.02	....	H	6	46 days
	37	F	N	...	....	H	...	31 days?
	68	F	W	4.57	....	N	...	4 mo.?
Beams & Harmos [4c]	32	M	...	7.11	18.9	H	6	Almost 1 yr.
Golden & Tullis [4d]	41	M	W	7.37	18.0	H	...	Years
	42	F	N	3.9	10.0	H	10	5 mo.
Callahan & others [4e]	55	M	W	4.8	15.9	N	4	More than 3 mo.
Rubin & others [4f]	44	F	...	...	....	N	...	$2\frac{1}{2}$ yr.
Golden & Bronk [4g]	63	M	W	...	10.8	N	3.4	Several years
	50	M	W	5.0	13.8	H	11	Few months
	50	M	W	5.8	15.4	H	10	Vague
Spain [4h]	66	F	W	...	....	H	8.0	7 yr.
	47	F	W	...	....	H	10.0	8 mo.
	59	M	W	...	....	N	4.0	1 yr.
	18	F	N	...	....	H	9.0	$2\frac{1}{2}$ mo.
	47	M	W	...	....	H	11.0	6 mo.
	34	F	W	...	....	H	12.0	?
	23	M	N	...	....	N	4.0	2 mo.
Katz & Auerbach [4i]	51	M	...	4.3	14.2	H	...	36 mo.
Heppleston [4j]	25	F	...	...	....	H	...	17 mo.
Peabody & others [4k]	47	F	...	...	....	..	...	2 yr.

* H = hypertrophy, N = normal.

rapid pulse rates are more often than not terminal changes and appear to be associated with final episodes of pneumonitis superimposed on the underlying lesions.

It appears that the tendency toward the development of cor pulmonale and polycythemia is latent within this disease.

PATHOLOGICAL CONSIDERATIONS

Pathologically, the disease has been recognized, in the 23 cases summarized in the Table, as a process involving the interstitial tissues of the lung manifest by alveolar wall hypertrophy. Such thickenings have been assumed to be fibrotic by, among others, one of us in reporting two cases previously.[4d] Reexamination of the lesions and closer study of these three cases by the methods stated above redefines the lesion as diffuse, but not necessarily universal, alveolar wall hypertrophy on the basis of capillary increase within these walls. The capillaries are much more numerous and much larger than normal and tend to depart markedly from their normal distribution on the alveolar surfaces. This angiosis is accompanied by abundant reticular

hyperplasia. For all practical purposes, the thickened alveolar walls represent the summation of these two processes. No other changes need be present at the time of death, as demonstrated in our Case 1, in which there were cor pulmonale and mild polycythemia.

The addition of collagen to make a true interstitial fibrosis of the lungs occurs, but it tends to be focal rather than diffuse and does not obscure the fundamental vascular and reticular hyperplasia.

Hamman and Rich [2] described one of their four cases as showing acute interstitial mononuclear and eosinophilic infiltration. We have encountered such instances but have no way of distinguishing them from forms of acute interstitial pneumo-

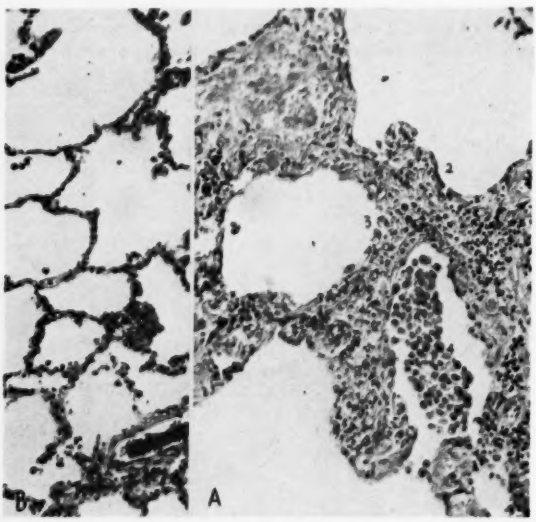

Fig. 4.—*A*, section from Case 2, showing great hypertrophy of alveolar walls, marked capillary proliferation, and the addition of collagen strands interstitially. Mild round cell infiltration is disposed characteristically in a small interstitial focus (1). Prominence of alveolar lining cells is present at (2) and (3). The cell clusters at (4) are anthracotic laden phagocytes. Note that the air spaces in Figures 3 and 4 contain no exudate. *B*, section from a normal lung for comparison. The magnifications are the same. Masson trichrome stain; × 100.

nitis.[5] Consequently, such cases are not included in this series. It was suggested by Golden and Tullis [4d] and Katz and Auerbach,[4l] among others, that diffuse interstitial fibrosis of the lungs may be a sequel to one or more attacks of acute interstitial pneumonitis or primary atypical pneumonia, when such lesions heal by organization rather than resolution. There is no proof to date of that hypothesis.

The degree of leucocytic participation in this lesion is very small. Instances of lymphocytic, monocytic, and even slight eosinophilic accumulations are encountered, but they are focal and do not contribute materially to alveolar wall hypertrophy.

As a rule, the alveolar air spaces are free except for variable numbers of anthracotic stippled phagocytes and occasional pools of fluid. Columnar and even squamous

5. Golden, A.: Pathologic Anatomy of "Atypical Pneumonia, Etiology Undetermined": Acute Interstitial Pneumonitis, Arch. Path. **38**:187-202 (Oct.) 1944.

metaplasia of alveolar linings are also present, rarely profound, never universal. The presence of frank bronchopneumonia appears to be a terminal phenomenon accompanied by fever as in our Case 3.

Interference with pulmonary oxygenization is manifest clinically by cyanosis, dyspnea, orthopnea, and sometimes polycythemia, and that there is interference with pulmonary circulation is shown by the development of a cor pulmonale. Figures 4 and 5 demonstrate that these proliferated capillaries in the alveolar walls create their own barriers to surface oxygenization. The addition of heavy reticulin fiber coats (Fig. 3) further decreases their atmospheric contact. Pulmonary hemodynamics must be altered by the greatly increased capillary bed area. The addition of

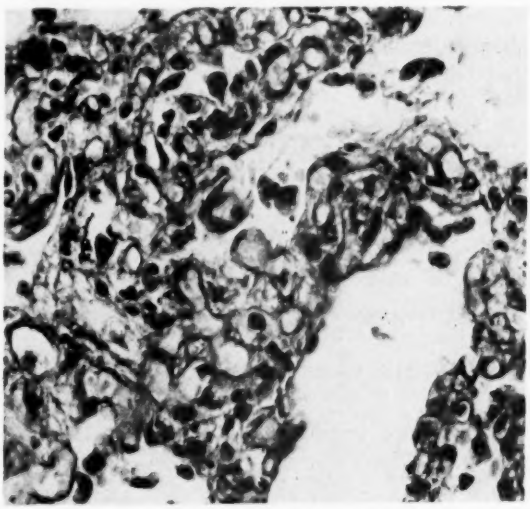

Fig. 5.—The proliferated capillaries in alveolar wall hypertrophy are outlined clearly by their basement membranes. The capillaries are much more numerous and of much wider diameters than normal; from Case 2. McManus-Schiff stain; × 400.

even variable amounts of collagen fibers, even if they are not universally distributed, must also play a part in interfering further with gaseous exchange.

When edema fluid and even fibrin are present in occasional alveolar lumens without evidence of specific pneumonitis, it seems reasonable to assume that leakage from such distended capillaries has taken place.

ETIOLOGY

The etiology of this malady remains obscure. There are no consistent histories nor findings of exposures to dusts or other noxious inhalants. A search of the lungs in Cases 1 and 2 under crossed Nicol prisms revealed no crystals of any kind.

The lesions in the lung must be differentiated from the not dissimilar ones of chronic passive congestion of long standing. None of the cases reported showed any significant hemosiderosis, such as is encountered in chronic passive congestion. None of the reported cases included known causes of chronic passive congestion such as mitral valvular disease. The fibrotic manifestations in the lungs of patients with

systemic scleroderma are collagenous rather than fundamentally vascular, as in this series. In none of the reported cases is there any indication of scleroderma or allied disorders, such as Raynaud's disease. There are changes in interstitial collagenization of the lung framework following x-ray treatment of the lungs which are similar but not identical to these lesions. The more detailed pathological points of differentiation will be taken up in a forthcoming report.

There is universal agreement that neither stainable bacteria nor inclusion bodies are demonstrable in these lesions, a negative finding with which we concur.

CONCLUSIONS

1. A review of the literature and our experience indicate that this diffuse bilateral pulmonary disease, of a specific type, in adults is characterized clinically by the development of dyspnea, cyanosis, and cough. There is a tendency toward the development of the symptoms and signs of cor pulmonale and, to a lesser extent, of polycythemia.

2. Pathologically, this condition is characterized by diffuse alveolar wall hypertrophy on the basis of marked capillary proliferation. This angiosis plus reticulum hyperplasia is limited to the alveolar walls and accounts for their thickness. The addition of collagen in such hypertrophic walls is variable; it may be absent and is usually focal rather than widespread.

3. The etiology of the lesion is unkown.

4. The disease is chronic, apparently progressive, and in fatal cases bilateral and diffuse.

5. The recognition of this entity with certainty is by pathologic diagnosis at present.

6. The disease designated originally as acute interstitial fibrosis of the lungs proves to be progressive diffuse alveolar hypertrophy of a specific reticuloangiotic type.

ORAL USE OF HYDROCORTISONE (COMPOUND F) IN TREATMENT OF SPRUE

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THIS STUDY is concerned with the effects of hydrocortisone (compound F) in patients with intractable primary sprue. Two forms of this steroid were used, the acetate and the free alcohol. While hydrocortisone acetate proved ineffective, the free alcohol of hydrocortisone, given orally, was found to be a valuable therapeutic agent in the management of these patients. The study represents an extension of our previous observations on the effects of corticotropin and cortisone acetate in sprue.[1]

SELECTION OF PATIENTS

The diagnosis of primary sprue was based on the typical symptoms and signs of this disorder, namely, diarrhea and steatorrhea, weakness, considerable weight loss, soreness of mouth and tongue, anemia, and polyavitaminosis; the condition was associated in some instances with hypocalcemia, tetany, osteoporosis, and hypoproteinemia. In none of these patients was there evidence of pancreatic disease, and results of pancreatic enzyme studies, when performed, proved to be essentially normal. Roentgen studies failed to reveal evidence of organic disease in the gastrointestinal tract, as may be seen in secondary sprue.[1a]

Many patients of this series showed at some time excellent or partial improvement on a sprue regimen consisting of high protein diet, with limitation of fats and polysaccharides, supplemented with adequate doses of liver extract, vitamin B_{12}, and folic acid.[2] In other patients no remission could be achieved; despite a seemingly satisfactory correction of the hematic status, diarrhea, steatorrhea,

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Read before the joint meeting of the Section on Gastroenterology and Proctology and the Section on Pathology and Physiology at the 102nd Annual Session of the American Medical Association, New York, June 4, 1953.

1. (*a*) Adlersberg, D., and Schein, J.: Clinical and Pathologic Studies in Sprue, J.A.M.A. **134**:1459, 1947. (*b*) Adlersberg, D.; Colcher, H., and Drachman, S. R.: Studies on the Effects of Cortisone and Pituitary Adrenocorticotropic Hormone (ACTH) in the Sprue Syndrome, Gastroenterology **19**:674, 1951. (*c*) Colcher, H.; Drachman, S. R., and Adlersberg, D.: Management of Intractable Sprue with Cortisone and Adrenocorticotropin (ACTH), Ann. Int. Med. **38**:554, 1953.

2. Adlersberg, D., and Rabinowitz, D.: The Sprue Syndrome: Improved Dietary Management, J. Am. Dietet. A. **26**:879, 1950.

weakness, and malnutrition persisted, resulting in chronic invalidism. Finally, there were patients in whom after many years of satisfactory response to accepted sprue therapy resistance to this therapy developed and others who even in the early phases of sprue proved refractory to intensive courses of treatment. It is well known that the prognosis of patients with intractable sprue is bad; their condition may deteriorate progressively to fatal termination.[3] Because of these considerations six patients of this group had been treated with prolonged courses of cortisone and/or corticotropin, as was previously reported.[1b,c]

The characteristic clinical and laboratory data of this series are presented in Table 1. There were 3 men and 14 women. Their ages ranged from 30 to 70 years, average 49. The duration of symptoms varied from 2 to 45 years, average 12. All patients appeared at some time chronically malnourished and presented evidence of considerable loss of weight, which varied from 11 to 73 lb. (4.9 to 32.9 kg.), average 32 lb. (14.4 kg.). In addition, weakness, anorexia, diarrhea, and distention were the outstanding features. The daily number of stools varied from 2 to 20. Four patients had clinical manifestations of tetany, and two had purpura. Despite therapy, almost all patients showed anemia, with hemoglobin concentrations varying from 7.9 to 13.4 gm., average 10.9 gm., and red cell counts of 2,500,000 to 4,800,000, average 3,600,000. Five patients exhibited hypoprothrombinemia, and five had hypocalcemia. The serum albumin concentration was 3.1 to 4.2 gm. in nine patients, 2.1 to 3 gm. in six; only two patients had serum albumin of 1.9 and 2 gm. per 100 ml., respectively. The level of vitamin A in the serum in the fasting state was very low; only three patients had a level of over 40 γ, two between 30 and 39 γ, three between 20 and 29 γ, and the remaining nine had levels below 20 γ per 100 ml. Similarly, the carotene levels in the serum were with one exception strikingly low, 1 to 43 γ per 100 ml., average 15 γ. The exception was Patient 9, who on repeated occasions and while under treatment with massive doses of folic acid and vitamin B_{12} showed a high concentration, of 420 γ per 100 ml. The vitamin-A-tolerance test was flat in 15 patients; in two patients (Patients 9 and 11) there was moderate elevation of the vitamin A serum level after ingestion of a standard dose of 180,000 I. U. of vitamin A in oil. The oral glucose-tolerance test (100 gm. glucose) was typically flat in all 15 patients for whom it was performed; in contrast, these patients presented normal curves when dextrose was administered intravenously (50 ml. of a 50% solution). Steatorrhea was present in all patients; the fecal fat concentration ranged from 31.3 to 60.5% of the dry material. Roentgen studies of the small bowel presented the characteristic findings of the "sprue pattern" in 15 instances, while 1 patient exhibited a milder degree of disturbance termed "sprue-like pattern" [4] and 1 was normal.

EFFECTS OF HYDROCORTISONE ACETATE

The first therapeutic trials were made with hydrocortisone acetate. It was administered in seven courses to five patients who, refractory to accepted sprue therapy, had received prolonged courses of cortisone and/or corticotropin therapy. The maintenance dose of the drug was established in each instance by careful "clinical titration." The results of replacement of cortisone or corticotropin by hydrocortisone acetate are summarized in Table 2. Observations of Patient 1 will serve as an illustration for this group.

CASE 1.—P. S. was a 55-year-old white man whose diarrhea and whose weight loss had started at the age of 32. The diagnosis of sprue was established 14 years later and was confirmed during repeated admissions to the Mount Sinai Hospital. His maximum weight loss was 40 lb. (18 kg.). One of the chief manifestations of his disorder was severe purpura caused by marked hypoprothrombinemia; another important feature was severe osteoporosis.

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3. Glazer, I., and Adlersberg, D.: Volvulus of the Colon: A Complication of Sprue, Gastroenterology **24**:159, 1953. Adlersberg and Schein.[1a]

4. Adlersberg, D.; Marshak, R. H.; Colcher, H.; Drachman, S. R.; Friedman, A. I., and Wang, C. I.: The Roentgenologic Appearance of the Small Intestine in Sprue: Long-Term Studies with Special Reference to Differential Diagnosis, Gastroenterology, to be published.

TABLE 1.—*Clinical and Laboratory Data*

				Symptoms and Signs					Laboratory Findings									
Patient No.	Sex	Age, Yr.	Birthplace	Duration, Yr.	Wt. Loss, Kg.	Stomatitis and Glossitis	Abdominal Distention	Stools/Day	Hb., Gm. (RBC, Million)	Serum A./G., Gm./100 Cc.	Serum Ca, Mg./100 Cc.	Serum Vit. A, γ/100 Ml.	Vit.-A-Tolerance Curve	Serum Carotene, γ/100 Ml.	Oral Glucose-Tolerance Curve	Fecal Fat (F. A.)*	X-Ray of Small Intestine†	Remarks
1	M	54	Poland	21	18.0	0	+	2-4	12.8 (3.6)	4.1/2.9	9.1	10	Flat	8	Flat	62.4 (23.6)	S. P.	Hospitalized previously for severe purpura
2	M	36	Canada	3	32.8	0	+	4-6	11.0 (3.8)	3.0/2.7	9.2	31	Flat	5	Flat	46.1 (28.4)	S. P.	.....
3	F	30	U. S. A.	8	18.0	0	+	4-14	12.1 (4.2)	1.9/2.4	7.7	48	Flat	15	Flat	40.6 (27.8)	S. P.	Had two normal pregnancies while on liver therapy, with postpartum relapses; had symptoms of tetany
4	F	46	Russia	4	23.9	+	+	10-12	10.0 (3.2)	3.2/3.3	8.9	14	Flat	17	Flat	60.5 (53.9)	S. P.	Had abdominal exploration in another hospital with negative findings
5	F	70	Russia	17	17.5	+	+	2-3	8.0 (2.7)	2.0/1.6	6.6	15	Flat	38	Flat	56.5 (39.9)	S. P.	Hemorrhagic manifestations twice, resistant to, vitamin K, responded to blood transfusions
6	M	57	Italy	10	11.2	0	+	5-6	12.4 (4.3)	2.3/3.7	10.2	7	Flat	19	Flat	48.1 (12.7)	S. P.	Old rightsided hemiplegia
7	F	43	U. S. A.	10	8.6	+	+	4-7	11.8 (4.0)	3.5/2.5	9.3	22	Flat	1	....	50.4 (34.4)	S. L. P.	.....
8	F	42	Italy	15	5.4	+	+	5-8	11.0 (3.8)	3.3/2.2	6.8	12	Flat	17	....	33.8 (22.1)	S. P.	Had episodes of tetany
9	F	59	Yugoslavia	9	15.3	+	+	8-12	11.2 (3.9)	3.6/3.3	9.4	41	N	420	Flat	11.2 (1.4)	N	.....
10	F	36	U. S. A.	8	5.0	0	+	10-15	11.5 (3.8)	3.9/2.3	8.5	0	Flat	43	Flat	40.0 (27.3)	S. P.	.....
11	F	39	Poland	11	8.1	+	+	6-10	8.0 (2.6)	3.7/2.8	8.8	14	35	8	Flat	....	S. P.	Received numerous blood transfusions in another hospital
12	F	65	Austria	2	18.0	+	+	4-5	7.9 (2.5)	3.0/2.9	4.9	21	Flat	16	Flat	54.9 (27.6)	S. P.	Episodes of tetany while under antianemic therapy
13	F	47	U. S. A.	28	6.7	0	+	6-10	10.7 (3.7)	.....	8.8	46	Delayed	30	Flat	31.3 (19.0)	S. P.	.....s....
14	F	46	U. S. A.	45	17.1	0	+	15-20	12.9 (4.8)	2.6/3.0	8.7	29	Flat	0	Flat	67.3 (19.4)	S. P.	Had episodes of tetany
15	F	42	U. S. A.	23	18.0	+	+	10-12	9.5 (3.6)	2.7/1.7	6.9	6	Flat	3	Flat	50.0 (21.0)	S. P.	Complicated by volvulus of cecum, surgically relieved
16	F	63	Austria	12	17.6	+	+	4-12	12.0 (3.5)	4.2/3.5	11.4	36	Flat	15	Flat	52.9 (36.0)	S. P.	Hyperthyroidism developed during standard sprue treatment; controlled medically
17	F	55	U. S. A.	7	7.2	+	+	6-8	13.4	2.9/2.2	...	15	25	6	Flat	....	S. P.	Tendency to skin petechiae

* Values are expressed as percentage of dry fecal weight; the first figure represents total fecal fat content, the second (in parentheses) the fatty acid fraction.
† S. P. = sprue pattern; S. L. P. = sprue-like pattern; N = normal.

TABLE 2.—*Repeated Courses of Therapy with Cortisone Acetate, Corticotropin, Hydrocortisone Acetate, and Hydrocortisone Free Alcohol in Five Patients with Therapy-Resistant Sprue (Group 1)*

Patient No.	Course of Therapy	Drug*	Duration, Days	Daily Dose			Wt., Kg.	Stools/Day	Fecal Fat (F. A.)†	Vit.-A-Tolerance Test, Serum Levels, γ/100 Ml.		Serum Carotene, γ/100 Ml.	Serum A/G, Gm./100 Cc.	Remarks
				Initial	Average	Final				Fasting	Peak			
1	1	Cortisone, O	95	50	35	12.5	54.4	1	.....	12	12	10	.....	Remission
	2	Hydrocortisone acetate, O	5	80	80	80	50.9	3-4	.....	5	..	4	.....	Relapse in 5 days
	3	Hydrocortisone acetate, I	14	125	125	125	48.6	5-6	54 (30)	5	..	7	.....	Full relapse
	4	Hydrocortisone free alcohol, O	65	80	35	15	54.4	1	46 (30)	8 22	27	8 12	.....	Full remission
	5	Hydrocortisone acetate, O	20	50	65	100	52.2	2-3	45 (21)	0	..	6	.....	Relapse, night blindness
	6	Hydrocortisone free alcohol, O	28	60	35	20	57.2	1	.....	11	..	7	.....	Remission
	7	None	34	0	0	0	53.1	2-3	.....	0	..	..	.....	Recurrence of diarrhea in 1 wk.
	8	Hydrocortisone free alcohol, O	122	40	25	20	56.2	1	40 (24)	20 6	..	10 10	.....	Remission
2	1	Cortisone, O	260	100	45‡	50	67.5	1	24 (8)	15	..	46	4.0/2.1	Remission
	2	Hydrocortisone acetate, O	42	40	45	100	63.0	2	34 (10)	..	..	..	.....	Relapse
	3	Cortisone, O	152	100	60	50	66.6	1	25 (9)	..	..	..	.....	Remission
	4	Hydrocortisone free alcohol, O	35	50	50	50	64.8	1	.....	12	..	37	.....	Remission
	5	Cortisone, O	70	75	55§	50	66.1	1	26 (12)	17	..	34	.....	Remission
	6	Hydrocortisone free alcohol, O	72	50	50	50	64.8	1	.....	6	..	38	.....	Remission
3	1	Cortisone, O	292	100	45	25	54.9	1	30 (17)	23	23	62	3.9/2.5	Remission
	2	Hydrocortisone acetate, O	20	100	100	100	52.6	5-6	25 (14)	..	..	..	.....	Relapse
	3	Cortisone, O	322	100	45‖	25	53.5	1	.....	20	..	102	.....	Remission
	4	Hydrocortisone free alcohol, O	33	50	30¶	30	54.0	1	.....	18	..	100	.....	Remission
4	1	Corticotropin-gel, I	125	50	50#	60	63.9	1	30	39	..	240	4.7/2.6	Remission
	2	Hydrocortisone acetate, O	33	100	100	100	60.3	3-6	.....	..	..	..	.....	Full relapse
	3	Hydrocortisone free alcohol, O	5	100	80	75	63.0	1	.....	..	..	..	.....	Remission
	4	Corticotropin-gel, I	13	40	25	40	62.5	1	.....	..	..	..	.....	Remission
	5	Hydrocortisone free alcohol, O	136	50	30**	30	63.5	1	34 (23)	35	..	22	.....	Remission
5	1	Corticotropin-gel, I	157	80	50††	40	45.9	1	36 (20)	40 65	98	63 55	4.3/3.8	Remission
	2	Hydrocortisone acetate, I	26	50	55	75	44.5	1-2	58 (21)	31	45	18	.....	Relapse
	3	Corticotropin-gel, I	112	80	45	20	48.6	1-2	40 (28)	42	68	165	.....	Remission
	4	Hydrocortisone acetate, O	98	80	35	30	47.2	1	.....	..	..	..	.....	Remission

* O = orally; I = injected.
† See the first footnote to Table 1.
‡ Patient was maintained for two weeks on 25 to 37.5 mg. of cortisone daily.
§ The dose of cortisone was occasionally raised to 75 or 100 mg. daily.
‖ Occasionally the dose of cortisone was increased to 100 mg. and then gradually reduced.
¶ Patient was maintained for several days on 25 mg. a day.
# The minimal dose used was 25 mg. This dose was raised on occasions to 40 and 60 mg. daily.
** The lowest dose was 20 mg.
†† The dose was raised to 120 mg. for nine days.

For one and one-half years prior to this study the condition of the patient was maintained on almost continuous cortisone or corticotropin therapy, in addition to standard antianemic therapy, which resulted in disappearance of diarrhea, gain of 15 lb. (6.7 kg.), and improvement of various chemical abnormalities (hypocalcemia, hypoproteinémia, etc.).

Prior to the use of hydrocortisone acetate the condition of the patient had been satisfactorily maintained for 95 days with cortisone by mouth in an average daily dose of 35 mg. (Course 1); the initial daily dose, of 100 mg. of cortisone, was gradually reduced to 12.5 mg. The body weight averaged 121 lb. (59.4 kg.) during this course, and there was one formed stool daily.

The replacement of orally administered cortisone acetate by orally administered hydrocortisone acetate in daily doses of 80 mg. (Course 2) resulted in a loss of 8 lb. (3.6 kg.) within five days, reappearance of 3 to 4 bowel movements daily, striking weakness, and other evidences of relapse.

After the patient was readmitted to the hospital, hydrocortisone acetate was administered by intramuscular injections for an additional 14-day period in doses of 125 mg. daily (Course 3). Nevertheless the patient's condition continued to deteriorate, the diarrhea increased to 5 to 6 bowel movements daily, the body weight decreased by an additional 5 lb. (2.3 kg.) to the lowest level, 108 lb. (48.6 kg.); the patient presented all the characteristic features of severe relapse.

At this time, hydrocortisone free alcohol was given orally with very satisfactory effect (Course 4). The initial daily dose was 80 mg. With this medication the diarrhea stopped promptly and appetite and vigor returned; the daily dose of the drug was gradually reduced to 15 mg. During the period of 65 days, with an average daily dose of 35 mg. hydrocortisone free alcohol given orally, complete control of symptoms was achieved; there was a gain of 13 lb. (5.9 kg.) and the patient presented the clinical picture of full remission. Nevertheless, the serum vitamin A level, although higher than before, was only 22 γ and the serum carotene level was 12 γ per 100 ml.

While in this excellent clinical condition the patient was subjected to a third trial with hydrocortisone acetate (Course 5), in which the final dose, of 15 mg. of orally administered hydrocortisone free alcohol, was replaced by 50 mg. of orally administered hydrocortisone acetate; this dose was then gradually raised to 100 mg. daily. During the 20-day period, with an average dose of 65 mg. hydrocortisone acetate per day, the patient lost 5 lb. (2.3 kg.), the frequency of bowel movements increased, and weakness, apathy, and other signs of relapse reappeared; the serum vitamin A level sank to indeterminable levels and the patient complained of night blindness.

A subsequent course of orally administered hydrocortisone free alcohol again proved to be very effective (Course 6). The initial daily dose of 60 mg. could be gradually reduced to 20 mg. In the course of 28 days, with an average daily dose of 30 mg. hydrocortisone free alcohol, the patient gained 11 lb. (4.9 kg.) and was able to resume his full-time job; there was one formed bowel movement a day.

Cessation of therapy led to relapse within several days, with reappearance of diarrhea and loss of 9 lb. (4.0 kg.) (Course 7). Such relapses had occurred previously in this patient (and in other patients of the group) whenever cortisone or corticotropin therapy was discontinued.

Since Jan. 15, 1953, the patient has been receiving uninterrupted therapy with orally administered hydrocortisone free alcohol (Course 8). On May 15, 1953, the required dose was 20 mg. (1 tablet, taken before breakfast). On this regimen the body weight returned to 125 lb. (56.3 kg.) and the patient is normally employed and works regularly; there is only one formed bowel movement daily.

COMMENT

The case history of a patient with therapy-resistant sprue has been presented. While hydrocortisone acetate given in three courses resulted in reappearance of diarrhea and other symptoms and signs of relapse, hydrocortisone free alcohol proved to be effective and adequately controlled the patient's symptoms.

Sprue in Patients 2 and 3 had been clinically controlled with average daily doses of 45 mg. of cortisone by mouth (Table 2, Course 1 in both patients). This dose of cortisone was replaced initially by 40 mg. orally administered hydrocortisone

acetate in Patient 2 (Course 2). Despite gradual increase of the daily dose to 100 mg. characteristic evidences of relapse, such as loss of 10 lb. (4.5 kg.), increasing weakness, and reappearance of abdominal distention and discomfort could not be prevented. In subsequent Courses 3 to 6, in which cortisone and hydrocortisone free alcohol were given orally, adequate clinical control was reestablished.

In Patient 3 the final daily dose of 25 mg. of cortisone by mouth (Course 1) was replaced by 100 mg. hydrocortisone acetate by mouth for 20 days (Course 2). Complete relapse, with loss of weight and reappearance of diarrhea, weakness, and anorexia were the result. In the following Courses 3 and 4 clinical control was easily maintained with cortisone or hydrocortisone free alcohol, both administered orally.

The disease in Patients 4 and 5 was maintained in clinical remission by uninterrupted courses of corticotropin-gel treatment for 125 and 157 days respectively. The replacement of corticotropin by hydrocortisone acetate in daily doses of 100 mg. in Patient 4 and by intramuscular injections of 50 to 70 mg. daily in Patient 5 resulted in relapse, while orally administered hydrocortisone free alcohol used in subsequent courses proved satisfactory.

It may be stated then that hydrocortisone acetate, used in two courses by intramuscular injection and in five courses by the oral route, resulted invariably in reactivation of sprue symptoms. This happened with doses of the drug considerably higher than the preceding or subsequent effective doses of cortisone, hydrocortisone free alcohol, or corticotropin. It was of interest, however, that relapses observed during the use of hydrocortisone acetate could be easily controlled by the other three drugs.

EFFECTS OF HYDROCORTISONE FREE ALCOHOL

Hydrocortisone free alcohol was administered to all 17 patients in 21 courses. For the purpose of this report the patients were divided in two groups.

Group 1 included the five patients whose conditions had been maintained for prolonged periods of time, up to three years, with either cortisone by mouth or parenteral corticotropin. They received, as already indicated, hydrocortisone acetate first and hydrocortisone free alcohol immediately afterwards, or after an interval of cortisone or corticotropin therapy.

The results obtained in nine courses of oral therapy of hydrocortisone free alcohol in Group 1 are summarized in Table 2. It may be seen that in three courses hydrocortisone free alcohol replaced orally administered cortisone, in two courses it replaced intramuscularly administered corticotropin-gel, in three courses it was administered at the height of relapse precipitated by the preceding administration of hydrocortisone acetate, and in one course it was given during relapse caused by interruption of hydrocortisone free alcohol therapy for 34 days (Table 2, Patient 1, Course 7).

Group 2 consisted of 12 patients who failed to respond satisfactorily to prolonged courses of intensive standard sprue therapy. The favorable therapeutic results obtained in Group 1 suggested the use of hydrocortisone free alcohol in these patients. It was used in 12 courses of oral therapy, and it was added to the basic therapy of these patients. Only one patient of this group (Patient 6) received corticotropin, which was then replaced by hydrocortisone free alcohol; the other patients received no adrenocortical therapy prior to the use of hydrocortisone free alcohol.

The initial daily dose of hydrocortisone free alcohol varied in Group 1 between 40 and 80 mg., while in Group 2, with one exception, the initial dose was 80 mg.

In both groups a remarkable change occurred in the patients' condition within two to seven days of treatment. They felt stronger and had an increased appetite;

TABLE 3.—*Results of Therapy with Hydrocortisone Free Alcohol in Twelve Patients with Therapy-Resistant Sprue (Group 2)*

Patient No.	Treatment*	Duration, Days	Daily Dose: Initial	Daily Dose: Average	Daily Dose: Final	Wt., Kg.	Stools/ Day	Fecal Fat (F. A.)†	Vit.-A-Tolerance Test, Serum Levels, γ/100 Ml.: Fasting	Vit.-A-Tolerance Test, Serum Levels, γ/100 Ml.: Peak	Serum Carotene, γ/100 Ml.	Serum A/G, Gm./100 Cc.	Remarks
6	Basic + corticotropin-gel, I	198	40	25	20	47.2	1-3	68 (45)	20 46	29	5 16	4.1/1.9	Remission
	Basic + hydrocortisone free alcohol, O	65	40	35‡	40	49.0	1-3	55 (37)	56	83	21	4.3/2.6	Remission
	Basic	36	..	..	..	49.0	8	62 (38)	..	..	..	.....	Relapse
	Basic + hydrocortisone free alcohol, O	19	60	35	10	48.1	1	.....	..	..	..	.....	Remission
	Basic	18	..	..	..	45.0	3-4	.....	3	12	1	3.7/3.0	Relapse
	Basic + hydrocortisone free alcohol, O	51	60	30	15	49.0	1	.....	35	..	9	.....	Remission
7	Basic	..	..	..	..	45.9	4-6	50 (34)	22	32	0	3.5/2.5	.....
	Basic + hydrocortisone free alcohol, O	123	80	35	30	51.8	1-2	39 (29)	20	28	70	.....	.....
8	Basic	..	..	..	..	49.5	5-8	43 (28)	12	16	17	3.3/2.2	.....
	Basic + hydrocortisone free alcohol, O	99	80	35	20	52.7	1	41 (28)	16	28	20	.....	.....
9	Basic	..	..	..	..	35.5	8-12	7 (4)	41	70	420	3.6/3.3	.....
	Basic + hydrocortisone free alcohol, O	99	80	45	30	41.9	0-1	10 (8)	..	..	..	.....	.....
10	Basic	..	..	..	..	40.9	4	40 (27)	0	22	43	.....	.....
	Basic + hydrocortisone free alcohol, O	91	80	45	40§	45.9	1	29 (17)	9	..	111	3.9/2.3	.....
11	Basic	..	..	..	..	51.3	6-10	4+	14	35	8	3.7/2.8	Mild glycosuria
	Basic + hydrocortisone free alcohol, O	90	80	45	40	55.3	1	20 (7)	..	..	..	.....	.....
12	Basic	..	..	..	..	40.5	3-4	55 (28)	21	26	16	3.0/2.9	.....
	Basic + hydrocortisone free alcohol, O	36	80	30	..	45.9	0-1	.....	..	..	..	.....	.....
13	Basic	..	..	..	..	45.0	4	31.3	46	..	30	Normal	.....
	Basic + hydrocortisone free alcohol, O	28	80	50	20	44.5	0-1	.....	..	..	..	.....	.....
14	Basic	..	..	..	..	42.7	2-5	67 (19)	29	38	0	2.6/3.0	.....
	Basic + hydrocortisone free alcohol, O	31	80	40	..	49.5	0-1	37 (30)	59	75	36	2.7/2.5	.....
15	Basic	..	..	..	..	50.4	5-6	48 (13)	7	18	19	2.3/3.7	.....
	Basic + hydrocortisone free alcohol, O	25	80	..	40	56.7	0-1	45 (34)	38	..	31	.....	.....
16	Basic	..	..	..	..	52.3	3-4	53 (36)	36	32	15	4.2/3.5	.....
	Basic + hydrocortisone free alcohol, O	24	80	..	50	53.4	6-1	.....	..	..	..	.....	.....
17	Basic	..	..	..	..	51.3	6-8	62 (49)	15	25	6	2.9/2.2	.....
	Basic + hydrocortisone free alcohol, O	19	80	..	50	57.2	0-1	57 (37)	46	58	56	.....	.....

* O = orally; I = injected.
† See the first footnote to Table 1.
‡ The dose was reduced to 20 mg. for two weeks and to 10 mg. for three days.
§ The dose was reduced for several days to 20 mg. but proved to be inadequate.

the apathy and weakness were replaced by a remarkable sense of euphoria and improved sense of well-being. The frequency of bowel movements diminished rapidly, and the stool showed normal consistency; with improvement of appetite and increased intake of food there was a steady increase in weight (Figs 1 and 2). The initial dose of the drug was maintained for 7 to 14 days and was then reduced, usually at weekly intervals, under steady control of weight, bowel movements, and general clinical condition. The 21 courses were given over a total of 1,394 days; each course lasted 5 to 136 days and the average duration was 66 days. The minimal effective maintenance dose of the drug was found to be 15 mg. daily in one course, 20 mg. in four courses, 25 mg. in one course, 30 mg. in four courses, and 40 and 50 mg. in two courses each; in five courses the time of treatment varied from 19 to 36 days and did not permit establishment of the minimal effective dose.

Gain in weight paralleled the improvement of the general condition. It varied from 2 to 15 lb. (0.9 to 6.7 kg.) and averaged 7 lb. (3.2 kg.) per course. The initial gain might have been caused in some instances by sodium and water retention, although all patients initially received a diet with limited sodium content. Ankle edema was occasionally present. Later in the course of therapy the weight gain was certainly the result of apposition of muscle and fat tissue.

The subsidence of diarrhea was another striking feature of this form of steroid therapy. In most instances the number of stools decreased to one a day. On occasion constipation developed for the first time after many years of diarrhea and called for considerable reduction of the daily dose of the drug; in a few instances small enemas and glycerine suppositories were needed.

Steatorrhea diminished considerably or was absent when large doses of the drug were used. As a rule, there was an inverse relationship between the dose of hydrocortisone free alcohol and the fecal fat content. Reduction of the dose resulted often in the reappearance of larger quantities of fecal fat. Patients whose condition was maintained on small doses of the drug exhibited at times considerable fat in their formed stools. It must be considered, however, that in these stages of therapy the patients' fat consumption amounted often to 100 gm. daily, while in the initial stages it was reduced to 30 to 40 gm.

The effects of hydrocortisone free alcohol upon the serum levels of vitamin A and the vitamin-A-tolerance test were similar to those observed during cortisone and corticotropin therapy.[1b,c] In several instances the flat vitamin-A-tolerance test was replaced by steeper or almost normal curves, e.g., Patient 1, Course 4 and Patient 6, Course 2; for other patients the curves remained flat although the fasting levels of vitamin A and carotene in the serum were significantly increased, indicating an improved but delayed absorption of vitamin A and carotene.

In patients with hypoalbuminemia a decided increase in the serum albumin was noted. Similarly patients who exhibited hypocalcemia showed a definite increase of serum calcium, to normal levels.

Serial roentgenologic studies of the small intestine were performed for many of these patients. Only occasionally was there a significant improvement of the sprue pattern under steroid therapy (Fig. 3). Roentgen interpretation of improvement was judged conservatively, because of the known variability of the roentgen findings in sprue. In most patients a marked discrepancy was noted between the degree of clinical improvement and the paucity of roentgen changes. Similar observations were made with cortisone and corticotropin.[4]

Fig. 1 (Patient 14).—*A*, patient before administration of hydrocortisone free alcohol; weight 95 lb. (42.7 kg.). *B*, after 31 days of therapy; weight 110 lb. (49.5 kg.).

Fig. 2 (Patient 14).—*A*, before therapy. *B*, after 31 days of therapy with hydrocortisone free alcohol.

It should be emphasized that the degree of improvement varied with each patient. Disappearance of diarrhea, considerable increase in weight, and ability to tolerate a normal bland diet was observed in 14 patients. In three patients the improvement was limited to a better sense of well-being, reduction of the number of stools, and moderate gains in weight.

OUTLINE OF MANAGEMENT

Administration of Hydrocortisone Free Alcohol.—The initial dose was usually 80 mg. daily, given orally in two to four equally divided doses. Maintenance doses of 20 to 30 mg. daily were as a rule given in one dose, half an hour before breakfast. The original dose was slowly reduced at intervals of 1 to 2 weeks by decrements of 10 to 20 mg. Dietary indiscretion resulted in episodes of diarrhea and required on occasion larger quantities of the drug for a few days. Higher

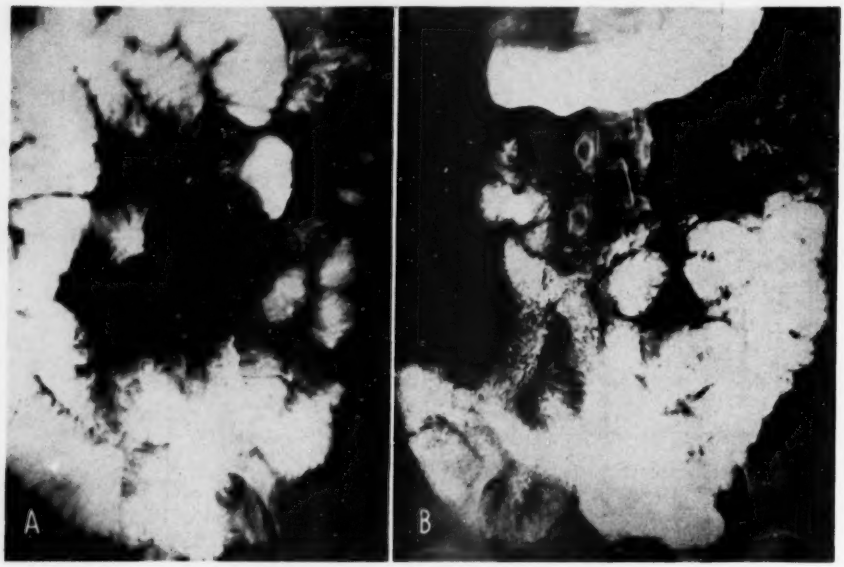

Fig. 3 (Patient 10).—*A*, small intestine pattern before hydrocortisone free alcohol therapy; note dilatation, segmentation, and hypersecretion. *B*, after three months of therapy; note improvement of pattern.

doses were also needed during intercurrent infections, emotional upsets, and other forms of stress. After clinical control was reestablished, reduction of the dose to maintenance levels was possible.

Diet.—Patients who were given this form of therapy in the hospital were placed on a low fat, high protein diet with limitation of starches; the sodium content was reduced to 500 mg. per day. In ambulatory patients the salt intake was limited to minimum but was not determined. However, when patients had improved satisfactorily to allow for smaller doses of the steroid (20 to 40 mg. daily) the sodium intake was liberalized to permit a more palatable diet. At this stage the restriction of fat and carbohydrate was found unnecessary in most instances and patients were allowed a bland low-residue diet with otherwise free selection of foods.

Additional Therapy.—During the treatment period the previous "basic" antianemic therapeutic regimen (liver extract, vitamin B_{12}, and folic acid, all administered by injection) remained unchanged. Potassium salts were administered when indicated in amounts of 3 to 6 gm. of potassium chloride daily or in 2 to 4 teaspoons (9.8 to 19.6 ml.) of liquid potassium triplex (potassium acetate, bicarbonate, and citrate). Patients with hypocalcemia or marked osteoporosis

were given calcium in the form of powdered calcium gluconate. Occasionally ammonium chloride was used for patients with tetany; when gross water retention was present this was administered with or without mercurial diuretics.

Complications.—These patients were examined at frequent intervals in order to detect any untoward effect of steroid therapy. Signs of Cushing's syndrome previously observed with the use of large doses of cortisone or corticotropin were not noted in this series, probably because of the therapeutic plan used. The policy was to reduce the dosage of the steroid, after the initial improvement, to minimal maintenance doses compatible with control of the clinical symptoms.

The detection and management of acute infections in sprue patients receiving steroid therapy is a challenging clinical problem. The low resistance of these patients to infections and stress is well known. In addition, the manifestations of infection may be masked by corticosteroid therapy. Therefore full attention should be given to minor symptoms and signs of infection.

Water retention and edema were occasionally seen in the initial stages of therapy when patients ingested excessive amounts of salt while receiving large doses of the drug. In these stages diuretics were administered. On the small maintenance doses of hydrocortisone free alcohol edema formation was not observed although the patients were allowed unlimited quantities of salt.

COMMENT

The role of the adrenal cortex in the mechanism of intestinal absorption [5] and in the etiology of sprue [6] has been extensively studied but has not been satisfactorily established. Anatomic changes of the adrenal cortex described in tropical sprue are essentially those of atrophy,[6b] as they may be found in conditions associated with emaciation and malnutrition; no characteristic or specific lesions were encountered in our previous postmortem studies of patients with nontropical sprue.[1a]

Nevertheless, clinical observation supports the concept that "diminished adrenocortical reserve" may play a role in certain instances of sprue. There may be in patients with sprue episodes of sudden superimposed acute diarrhea, severe loss of water and electrolytes, calf cramps, severe asthenia, and other signs resembling an Addisonian crisis. Pregnancy, usually well tolerated by patients with sprue in the first to second trimesters, may lead to severe relapse in the last trimester or after conclusion of pregnancy,[7] suggesting gradual exhaustion of the adrenocortical reserve during pregnancy. On the other hand, patients with Addison's

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6. (*a*) Verzar, F., and Laszt, L.: Nebennierenrinde und Fettresorption, Biochem. Ztschr. **278:**396, 1935. (*b*) Diéz Rivas, F.; Hernandez Morales, F., and Koppisch, E.: The Adrenal Gland in Tropical Sprue, J.A.M.A. **150:**647, 1952. (*c*) Culver, P. J.; Benson, J. A., and Jones, C. M.: The Effect of Pregnancy on Non-Tropical Sprue, read before the Annual Meeting of the American Gastroenterological Association, Atlantic City, N. J., May 2, 1953. Adlersberg and Schein.[1a]

7. Unpublished data. Culver, Benson, and Jones.[6c]

disease may present evidence of defective intestinal absorption, which can mimic sprue and can be corrected by cortisone.[1b] A functional insufficiency of the adrenal cortex in patients with intractable sprue may explain the observed therapeutic effects of cortisone, hydrocortisone, and corticotropin, while patients with Addison's disease may display features resembling those of sprue.

Evidence has been presented previously to suggest that cortisone and corticotropin when used in sprue improve the intestinal absorption of fat and fat-soluble vitamins.[1b,c] The diminished fat content, the higher levels of vitamin A and carotene in the serum, and the improved results of vitamin-A-tolerance tests observed in this series of patients treated with hydrocortisone free alcohol may be interpreted similarly. It must not be overlooked, however, that the well-known effects of the steroid hormones on mood and appetite may have contributed per se to the improvement.

Remissions achieved by the use of hydrocortisone free alcohol could not be maintained after discontinuation of the drug. This was seen in Patients 1 and 6, in whom 1 to 3 weeks after cessation of treatment clinical relapse occurred despite uninterrupted and unchanged administration of basic antianemic therapy. An attempt was therefore made to maintain the condition of patients with refractory sprue by continuous therapy with minimal effective doses by hydrocortisone free alcohol. The dosage was established for each patient by prolonged clinical titration in a manner similar to that previously used for cortisone and corticotropin.[1b,c] No adverse effects, no habit formation, and no resistance to this mode of therapy have been noted.

Hydrocortisone free alcohol offers certain advantages in comparison with cortisone and corticotropin. It is effective in small doses without producing undesired side effects. Similar observations have been made by those who have used this steroid in the therapy of rheumatoid arthritis.[8]

Additional observations in sprue will be necessary further to establish the therapeutic superiority of hydrocortisone free alcohol. One may reason perhaps that neither cortisone nor hydrocortisone are primarily involved in the mechanism of sprue and that other related compounds or analogues may prove in the future more effective in the management of sprue.

SUMMARY

Seventeen patients with the sprue syndrome were treated with two forms of hydrocortisone, the acetate and the free alcohol. Hydrocortisone acetate was used in 7 courses of therapy, and hydrocortisone free alcohol was used in 21 courses.

All patients exhibited various degrees of resistance to standard sprue therapy. The average patient was 49 years old, had sprue for 12 years, showed loss of weight of 32 lb. (14.4 kg.), had a hemoglobin level of 10.9 gm. and a red cell count of 3,600,000. The patients were divided in two groups. Group 1 included five patients whose condition, because of intractability, had been maintained for periods up to three years with either cortisone by mouth or parenterally administered corticotropin (aqueous or gel). Group 2 consisted of 12 patients who failed to respond

8. Boland, E. W., and Headley, N. E.: Compound F Used Orally in Patients with Rheumatoid Arthritis, J.A.M.A. **148:** 981, 1952.

satisfactorily to prolonged courses of extensive conventional sprue therapy but who, with one exception, had received no corticosteroid therapy prior to the administration of hydrocortisone.

In Group 1 the replacement of cortisone or corticotropin by hydrocortisone acetate, administered orally in five and parenterally in two courses, in addition to "basic" antianemic therapy, resulted invariably in reappearance of diarrhea, steatorrhea, loss of weight, weakness, apathy, and other evidences of relapse.

In contrast, hydrocortisone free alcohol given orally to all 17 patients (Groups 1 and 2) was well absorbed from the gastrointestinal tract and promptly controlled the symptoms of sprue. Subsidence of diarrhea, weakness, and apathy; considerable gains in weight, and laboratory evidence of improved intestinal absorption were the chief evidences of clinical remission.

The oral administration of hydrocortisone free alcohol has no curative effects. The extent of remission varies with each patient. One to three weeks after cessation of this form of steroid therapy clinical relapses occurred despite continued administration of liver extract, vitamin B_{12}, and/or folic acid. An effort was therefore made to maintain therapy-resistant sprue patients on minimal doses of hydrocortisone free alcohol compatible with clinical control.

At present it may be stated that because of the need of only small maintenance doses and the apparent absence of adverse effects of such doses given over prolonged periods of time hydrocortisone free alcohol represents a valuable therapeutic agent in intractable sprue.

Dr. E. Alpert, Merck & Company, Inc., and Dr. David Klein, The Wilson Laboratories, provided hydrocortisone free alcohol and cortisone acetate, and corticotropin-gel, respectively. Helen Fung and Sarah Jane Baker gave technical assistance.

TREATMENT OF LEUKEMIA WITH TRIETHYLENE THIOPHOSPHORAMIDE (THIO-TEPA)

Preliminary Results in Experimental and Clinical Leukemia

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IT IS NOW nearly two hundred years since Horace Walpole coined the term serendipity, which he in part borrowed from the title of an old legend, the "Three Princes of Serendip," who, so the story goes, went forth into the world and made discoveries of things they were not in search of through "chance" or "sagacity." The results that we have to report may well be considered as gains from serendipity, for they indirectly derive from attempts started about six years ago to produce glandular gastric cancer in rats by inducing gastric ulcer and instilling methylcholanthrene daily into the stomach through a rubber catheter. No gastric cancers were produced in this manner, but instead from these experiments there developed two useful experimental tools, one, adenocarcinoma of the breast,[1] and the other, four types of leukemia. These leukemias include an acute lymphatic[2] and a chronic myelongenous (chloro) leukemia,[3] which have already been described, and an acute monocytoid myelogenous leukemia and a sarcoleukemia, which we have not as yet reported. All of these leukemias are transferable readily to very young (under 7 days of age) random-bred rats. The purpose of this communication is to present our preliminary experience in the treatment of two of these experimental leukemias, of

Research Fellow, Fels Research Institute (Dr. Sun).

Read before the Section on Experimental Medicine and Therapeutics at the 102nd Annual Session of the American Medical Association, New York, June 3, 1953.

From the Samuel S. Fels Research Institute and Temple University Hospital, Temple University School of Medicine, St. Christopher's Hospital and Einstein Medical Center, Northern Division.

1. Shay, H.; Aegerter, E. A.; Gruenstein, M., and Komarov, S. A.: Development of Adenocarcinoma of the Breast in the Wistar Rat Following the Gastric Instillation of Methylcholanthrene, J. Nat. Cancer Inst. **10**:255, 1949.

2. Shay, H.; Gruenstein, M., and Glazer, L.: Uniform Transfer to Random Bred Rats of Lymphatic Leukemia Induced by Gastric Instillation of Methylcholanthrene, Proc. Soc. Exper. Biol. & Med. **75**:753, 1950.

3. Shay, H.; Gruenstein, M.; Harris, C., and Glazer, L.: Transfer of Myelogenous Leukemia Induced by Gastric Instillation of Methylcholanthrene in Rats, Blood, **7**:613, 1952.

human leukemias and other malignant lesions of the hemopoietic system, as well as of inoperable nonleukemic malignant lesions with triethylene thiophosphoramide (Thio-TEPA),[4] whose possible usefulness was uncovered in the treatment of a number of experimental tumors,[5] including the chronic myelogenous (chloro) leukemia of the rat.

About two years ago, animals with the chloroleukemia were given to the Lederle Research Group, who have since transferred this leukemia to more than 4,000 rats which have served as test animals in their screening program of possible carcinolytic compounds.

Among the compounds tested was triethylene thiophosphoramide. Its configuration as well as its relation to methyl-*bis* (β-chloroethyl) amine hydrochloride (nitrogen mustard, HN_2) and some other ethylenimine derivatives that have been used clinically are shown below.

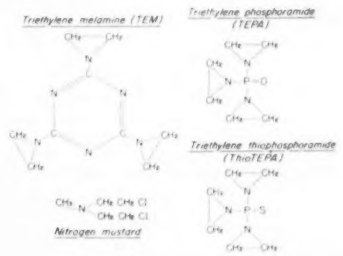

Fig. 1.—Chemical configurations of triethylene melamine, methyl-*bis* (β-chloroethyl) amine hydrochloride (nitrogen mustard), triethylene phosphoramide, and triethylene thiophosphoramide.

The Lederle investigators [5c] treated leukemic rats with triethylene thiophosphoramide intraperitoneally every other day until nine injections had been given. The first and second doses were 3 mg. per kilogram body weight and subsequent doses were 1.5 mg. per kilogram. Peripheral counts that ranged from 50,000 to 300,000 returned to normal levels of 10,000 within six days. However, differential smears might still reveal a few abnormal cells, and if treatment were discontinued entirely relapse would soon be apparent. When maintenance doses of the drug were administered at weekly intervals, the animals remained well and looked and behaved no differently from normal animals of the same age.

4. Dr. James Ruegsegger, Lederle Laboratories Division, American Cynamid Company, supplied the triethylene thiophosphoramide used in this study.

5. (*a*) Williams, J. H.; McKenzie, D.; Halliday, S.; Personeus, G. B.; Stevens, M. L.; Sparks, S. J.; Smith, S. G.; Troy, W. P.; Schurr, H. S.; Gleason, H. R.; James, E. R.; Moser, L.; Lydick, P.; Landes, M. J.; Eve, V.; Stick, P., and Vincent, N.: The Effect of a Series of Ethylene Amines Against Experimental Cancer, presented at the American Association for Cancer Research Meetings, New York, April 12, 1952. (*b*) Personeus, G.; Halliday, S. L.; McKenzie, D., and Williams, J. H.: Effect of a Series of Ethylenimine Derivatives Against Metastasizing Mammary Adenocarcinoma of the Rat, Proc. Soc. Exper. Biol. & Med. **81**:614, 1952. (*c*) Sparks, S. J.; Stevens, M. L.; Landes, M. J.; Halliday, S. L.; McKenzie, D., and Williams, J. H.: The Effect of a Series of Ethylenimine Derivatives on Myeloid Chloroleukemia in the Rat, to be published.

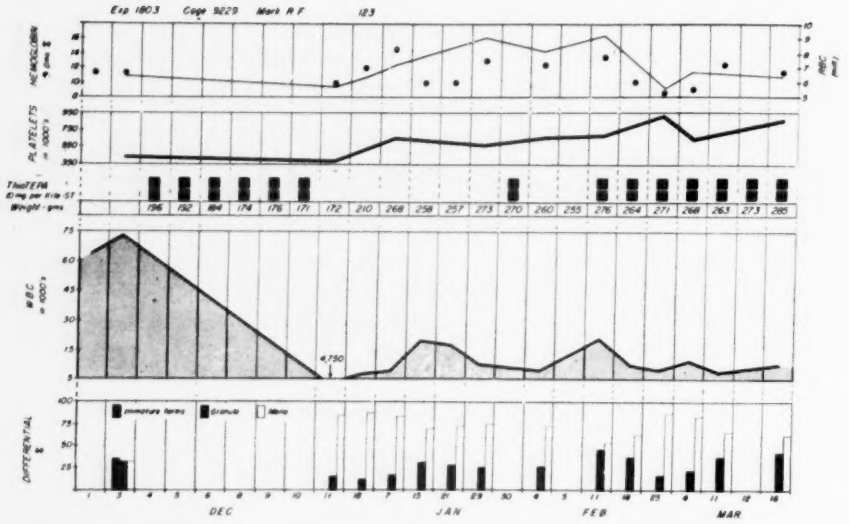

Fig. 2.—Hematologic response to oral therapy (initial and maintenance) with triethylene thiophosphoramide in a rat with chronic myelogenous (chloro) leukemia.

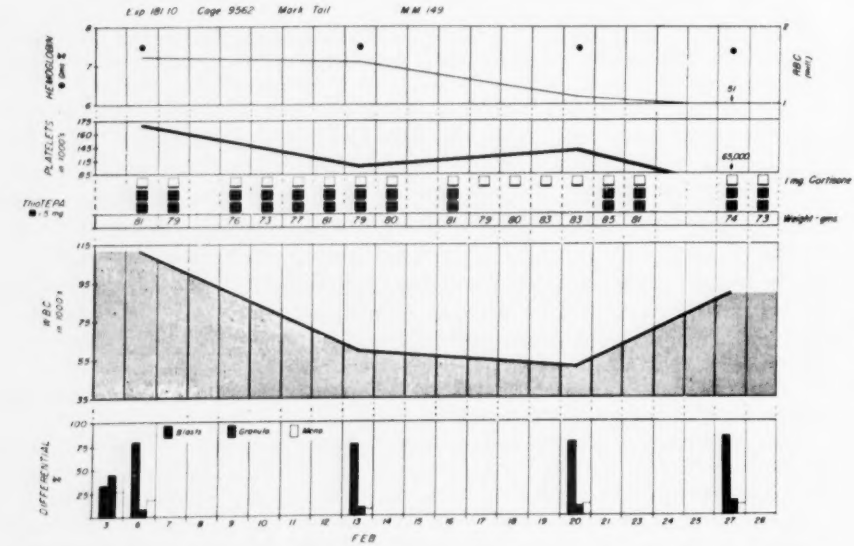

Fig. 3.—Failure of response to triethylene thiophosphoramide of rat with acute monocytoid myelogenous leukemia. The response of this leukemia and that of the chronic leukemia to this drug parallels the response of the acute and chronic leukemias in man.

About eight months ago, having been shown animals treated with triethylene thiophosphoramide that were alive and well seven months after the controls were dead,[6] we began trial of the drug clinically and in our two types of rat myelogenous leukemia.

It was our purpose to determine if the compound would be active when given by stomach catheter, in order to consider its suitability for oral administration clinically. Furthermore, having the two varieties of experimental myelogenous leukemia available, we might determine if their response to the drug would parallel results obtained in the acute and chronic varieties in man.

Figure 2 is illustrative of the results obtained in the treatment of animals with the chronic myelongenous (chloro) leukemia. It also shows the sustained effect of a

TABLE 1.—*Types of Malignant Lesions Treated with Triethylene Thiophosphoramide**

	Patients, No.
Acute blast cell leukemia	10
Myeloblastic crisis	1
Subacute myelogenous leukemia	1
Chronic myelogenous leukemia	7
Monocytoid myeloid leukemia	3
Chronic lymphocytic leukemia	7
Lymphosarcoma	3
Hodgkin's disease	3
Reticuloendotheliosis	2
Acute plasma cell leukemia	1
Multiple myeloma	1
Melanosarcoma	2
Breast carcinoma (recurrent with metastases)	2
Primary hepatoma	1
Carcinoma of esophagus	1
Carcinoma of lung	1
Linitis plastica	1
Diffuse abdominal carcinomatosis (primary site unknown)	1
Ewing's sarcoma	1
Total	49

* Patients in this table who showed a good or limited response to triethylene thiophosphoramide are shown in Tables 2 and 3.

weekly maintenance dose. The average life span of rats with this leukemia untreated in our colony has been nine and seven-tenths days.

Figure 3 is illustrative of the failure of the drug favorably to influence the course of the acute monocytoid myelogenous leukemia even when treatment was supplemented with cortisone. The average life span of untreated animals with the acute leukemia is eight days. The drug increased the life span in the treated group to only 19.5 days. The ability of triethylene thiophosphoramide to bring about an essentially normal peripheral leucocyte picture in the chronic form and its failure materially to alter the high percentage of blast cells in the acute form are strikingly demonstrated in the two charts. From the standpoint of suitability of these two leukemias as experimental tools, it is of especial interest that acute and chronic leukemias in man have shown essentially similar responses to this drug. The studies with the experimental leukemias will be reported in detail elsewhere.

6. Sparks, S. J.: Personal communication to the author.

Thus far, triethylene thiophosphoramide has been administered to 49 patients (Table 1). For all pretreatment bone marrow and peripheral blood studies, as well as routine laboratory examinations, were done. The blood studies were repeated daily, and bone marrow aspirations

TABLE 2.—*Patients Showing Good Response to Triethylene Thiophosphoramide (Thio-TEPA)*

Patient	Diagnosis	Age, Yr.	Sex	Total Dose, Mg.*	Period Since Treatment Started, Wk.	Comment
P. H.	Subacute myelogenous leukemia	11	F	255 I. M. 130 O. 65 I. V.	24	Good clinical and hematologic response; see case report
D. R.	Chronic myelogenous leukemia	53	F	265 I. V. 440 O.	14	Duration 3½ yr.; previous treatment urethan, x-ray 3 times, potassium arsenite, *p*-aminobenzoic acid, refractory; good clinical and hematologic response with Thio-TEPA
W. T.	Chronic myelogenous leukemia	60	M	360	11	Refractory to x-ray, urethan, and nitrogen mustard before Thio-TEPA was given; W. B. C. reduced from 100,000 to 6,400; spleen reduced; good clinical response
A. S.	Chronic myelogenous leukemia	50	F	165	21	Good clinical and hematologic response; no previous treatment
A. B.	Chronic myelogenous leukemia	32	M	38	3	Has undergone excellent hematological remission; see case report
T. L.	Chronic lymphatic leukemia	50	M	275 I. M. and I. V. 270 O.	25	Good clinical and hematologic response; see case report
A. F.	Chronic lymphatic leukemia	74	M	110	15	Striking reduction in tumor masses; good clinical remission; has remained in remission, no further therapy after first 30 days
S. S.	Chronic lymphatic leukemia	54	M	185	13	Refractory to x-ray, urethan; tumor masses and W. B. C. count reduced very effectively after 19 days treatment (185 mg.) but depression of marrow with anemia and thrombopenia developed; drug stopped; marrow recovered in about 30 days and patient is still in excellent remission
J. R.	Chronic lymphatic leukemia	62	F	145	15	Good clinical and hematologic remission; short period of thrombocytopenia with spontaneous correction
P. L.	Chronic lymphatic leukemia	74	M	35	6	No previous therapy; good remission after 6 days of Thio-TEPA and total dose of 35 mg.
N. W.	Hodgkin's disease	19	F	111	18	Excellent remission; see case report
H. L.	Chronic lymphatic leukemia	67	M	100	3	Refractory to x-ray and TEM†; with Thio-TEPA, tumor masses and W. B. C. count reduced strikingly (352,000 to 15,000); discharged from hospital 2/22/53 in good clinical and hematological remission; returned 3 days later with fulminating pneumonia and died
S. P.	Multiple myeloma	66	M	28	6	Complete relief from pain; gain of 1.8 kg.; no change in x-ray appearance of bone lesions this time
J. S.	Carcinoma, breast recurrence, metastatic	31	F	114	19	Disappearance of metastatic axillary nodes as well as recurrent skin nodule in operative scar
L. P.	Carcinoma, breast recurrence, metastatic	63	F	104	10	Decrease in size of axillary metastasis and nodules in scar

* I. M. = intramuscularly; I. V. = intravenously; O. = oral administration. Doses for which no route is indicated were given parenterally.
† TEM = triethylene melamine.

were done at appropriate intervals throughout treatment. Urinalysis and complete liver function profiles were obtained before treatment was started and at intervals during treatment.

Method of Treatment.—Triethylene thiophosphoramide is dissolved in sterile isotonic sodium chloride solution in a concentration of 10 mg. per cubic centimeter, sterilized by filtration through

a sintered glass filter, tested for sterility by culturing in thioglycolate medium, and stored in rubber-capped sterile vials at 5 C.[7] It has been administered to patients intramuscularly or intravenously, usually in doses of 2, 5, or 10 mg., the size of any one dose depending on the hematological findings in the course of treatment.

Intramuscularly it is administered undiluted. For intravenous use the amount of drug to be given is added to a 10 cc. vial of isotonic sodium chloride solution, the contents of which may then be injected in a period of two minutes without anticipation of any untoward reaction. Injections were given daily or at longer intervals. The intervals between injections were guided by the hematological response. The total dose of triethylene thiophosphoramide administered varied widely, depending on the condition being treated as well as upon the hematological response. Table 1 lists the types of disease and the number of patients with each treated. Tables 2 and 3 give a few details of those cases in which there was a good or a limited response to the drug.

TABLE 3.—*Patients Showing Limited Response to Triethylene Thiophosphoramide (Thio-TEPA)*

Patient	Diagnosis	Age, Yr.	Sex	Total Dose, Mg.	Period Since Treatment Started, Wk.	Comment
D. S.	Chronic myelogenous leukemia	11	M	285	12	Excellent initial results; treatment somewhat intermittent; acute myeloblastic crises; death in 5 days after development of acute phase from rupture of spleen
M. D.	Chronic myelogenous leukemia	60	F	90	2	Admitted to hospital virtually blind, could only distinguish light; W. B. C. 750,000; vision improved after 5 days of therapy and returned completely after 8 days; acute bilateral obstructive uropathy developed; autopsy, dilated ureters, pelvis and calyces filled with uric acid stones, obviously of fairly long duration and certainly not due solely to rapid cytolysis possibly contributed by the drug
L. L.	Chronic monocytoid myelogenous leukemia	63	F	150	15	Partial remission still in effect; Thio-TEPA being continued
M. C.	Acute myeloblastic crisis, chronic myelogenous leukemia	65	M	65	13	Good short remission with Thio-TEPA and cortisone; relapse 1/26/53, further therapy ineffective
F. R.	Acute stem cell leukemia	2	M	28	..	Partial clinical remission
H. C.	Hodgkin's disease	40	M	90	2	Striking decrease in size of softer lymph nodes; no effect on pain in right hip or on size of firm nodes; treatment inadequate, stopped at end of 2 weeks
A. C.	Chronic myelogenous leukemia ? myeloid metaplasia	59	M	118	12	Good clinical response and marked reduction of large firm spleen

RESULTS OF THERAPY

Subacute and Chronic Leukemias.—Triethylene thiophosphoramide appears to have its most favorable action in subacute and chronic leukemia.

Chronic Lymphatic Leukemia.—T. L., whose treatment was started on Oct. 24, 1952, was a 50-year-old white man with chronic lymphatic leukemia. He had noted progressive lymphadenopathy for one year, and weakness and easy fatigability for three months prior to his admission to Temple University Hospital. In recent months, he had had abdominal discomfort and epigastric fullness after meals. There was only slight weight loss, but episodes of profuse sweating were occurring with increasing frequency. A lymph node biopsy was taken at another hospital, where the diagnosis of lymphosarcoma was made.

The pertinent physical findings on his present hospital admission included a generalized lymphadenopathy, with walnut-sized masses of nodes in each axilla and a protuberant abdomen.

7. Dr. Morton Klein, Associate Professor of Bacteriology, prepared the sterile solutions of the drug.

The latter proved to be due to a firm upper abdominal mass that extended down to about 2 in. (5 cm.) below the umbilicus in the midline. Although the mass moved with respiration, it was obviously not the spleen and was thought to represent a large mass of abdominal lymph nodes.

The peripheral blood and marrow findings were interpreted as indicating a rather active chronic lymphocytic leukemia. In Figure 4 are summarized some of the pertinent hematological findings during the early period of treatment, to Dec. 7, 1952. Subsequently, he continued in excellent clinical and hematological remission on maintenance doses of the drug. Ten milligrams were given intravenously at two-week intervals if the white blood cell count rose above 12,000. Results of blood studies on April 20, 1953, were as follows: hemoglobin 15.3 gm., red blood cells 5,620,000, platelets 208,000, hematocrit level 50%, white blood cells 9,500. Results of liver function tests, consisting of serum bilirubin fractionation; cephalin-cholesterol, colloidal gold, thymol

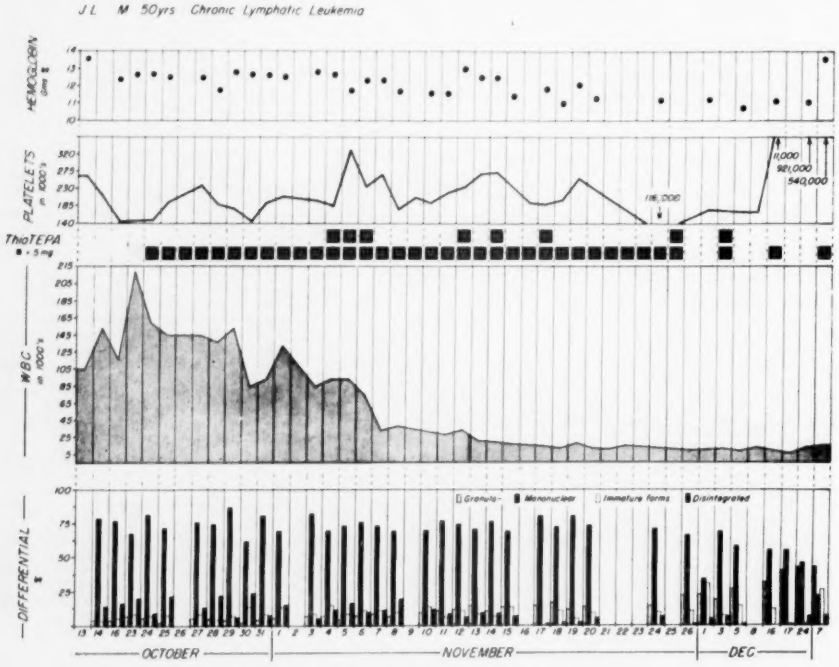

Fig. 4.—Hematologic response of patient with chronic lymphatic leukemia to treatment with triethylene thiophosphoramide.

turbidity, 18-hour turbidity ratio, and gamma globulin flocculation tests; determinations of serum alkaline phosphatase, total serum cholesterol and cholesterol esters, and sulfobromophthalein (Bromsulphalein) retention, were within normal limits at the time triethylene thiophosphoramide was started six months ago and have remained so when repeated after three months and six months of treatment.

This patient, when examined last for this report, on April 20, 1953, six months after treatment with triethylene thiophosphoramide was started, had no complaints, was eating well, had gained more than 13 lb. (5.9 kg.), from his low point of 122 lb. (54.9 kg.) while in the hospital, and had returned to his job for over four months. On physical examination nothing abnormal could be palpated in the abdomen and the large masses of axiliary lymph nodes were now represented by several discrete nodes in each axilla, with the largest one about the size of a small filbert kernel. For the past month, this patient has been maintained on oral therapy, a 10 mg. tablet once a day. He is apparently continuing in good remission on this regimen and has had no symptoms that might be attributed to taking the drug in this dosage.

Subacute Myelogenous Leukemia.—Patient P. H., a girl aged 11 years, was first admitted to St. Christopher's Hospital on Sept. 29, 1952, because of pain in the right hip which started about three weeks earlier and was so severe that the child could not walk. There were no other complaints. The blood count showed 360,000 white blood cells per cubic millimeter, and the tip of the spleen was felt 15.0 cm. below the costal margin. Bone marrow aspiration was done and showed the picture of a subacute myelogenous leukemia. Treatment with urethan, 0.75 gm. daily, was started and continued for 12 days with no appreciable therapeutic effect. The dose of urethan was increased to 1.5 gm. daily for 14 days more but without any improvement in the blood cell count or clinical picture. On Nov. 4, 1952, the spleen had not changed in size and the liver edge was palpable 1.5 cm. below the costal margin. On this day, triethylene thiophosphoramide was started. The dosage and hematological changes from Nov. 4, 1952, to Jan. 7, 1953, are shown in Figure 5. The child has shown an excellent response clinically; the pain in the hip disappeared

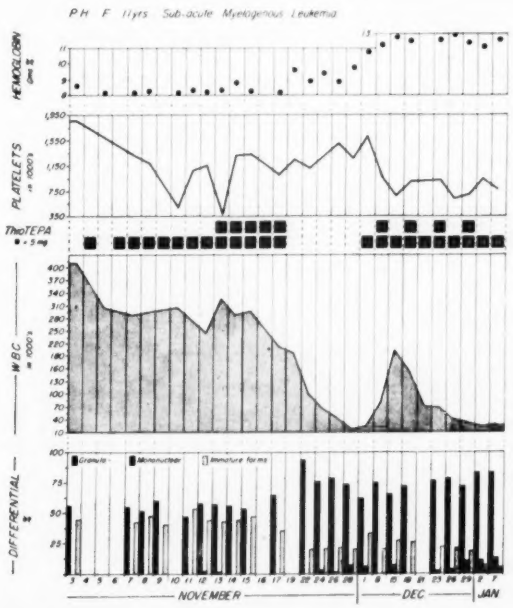

Fig. 5.—Hematologic response of patient with subacute myelogenous leukemia to treatment with triethylene thiophosphoramide.

five days after treatment with triethylene thiophosphoramide was started; she is now (April 24, 1953, when last examined for this report) normally active and has gained 14 lb. (6.3 kg.), while the tip of the spleen is palpable only about 2 cm. below the costal margin and the liver edge is no longer felt. She has been back at school taking a full schedule including play period for the past five months. Results of blood studies at this time (April 24, 1953) are hemoglobin 13.2 gm.; white blood cells 16,800 per cubic millimeter; platelets 556,000, and the differential cell count 87% granulocytes, 3% immature forms, and 13% mononuclear cells. She has continued on maintenance doses of triethylene thiophosphoramide, 10 mg. intramuscularly approximately once a week. She was placed on oral therapy for a short time, but this did not keep her leukemia under control. On March 28, her white blood cell count was 13,150. She was given a 10 mg. tablet orally every 3rd day, and 8 days later, on April 6, the count was 16,800. The oral dose was increased to 10 mg. every other day, and on April 11 the white blood cell count rose to 42,450. The dose was then increased to 20 mg. triethylene thiophosphoramide daily for five days. While the white blood cell count on April 16 showed a decrease to 33,000, the larger dose of drug had caused vomiting. On April 16 the patient was given 15 mg. intramuscularly without

any immediate reaction, and on April 24 the white cell count was again down to 16,800. It is significant that in this child, who has now been under treatment for six months, the leukemia shows no indication of escaping from control by the drug, even though on two occasions in the course of treatment inadequate therapy was accompanied by a sharp rise in white cell count. The patient is now back on her intramuscular 10 mg. maintenance dose once a week.

The case of A. B., a man aged 30 years, illustrates how rapidly changes in a chronic myelogenous leukemia may be produced with this drug. In January, 1951, he noticed a bruise on his chin which remained for about a week. About the same time, fatigue developed, and in February, 1951, the patient's wife noticed that his abdomen was enlarged. However, a blood cell count was not done until July 1951. It showed a white cell count of 200,000, and a diagnosis of chronic myelogenous leukemia was made. Since then the patient has received P^{32}, sodium pteroyl

TABLE 4.—*Dosage of Triethylene Thiophosphoramide (Thio-TEPA) and Results of Blood Studies in Patient A. B., with Chronic Myelogenous Leukemia*

Date	Thio-TEPA, Mg. I. V.	R. B. C., Million	HB., Gm.	Ht., %	Ret., %	W. B. C.	Bands, %	Segs., %	Lymphocytes, %	Monocytes, %	Basophiles, %	Eosinophiles, %	Disintegrated, %	Juv., %	Myelocy. Neutros., %	Blasts, %	Promyelocytes, %	Atypical Lymphs., %	Platelets
4/ 2/53*	10	4.03	12.1	40	2.6	65,000	24.5	31	0.5	2	2.5	0.5	14.5	8.5	15.5	0.5	...	...	302,000
4/ 3/53	10	....	....	..	...	70,000	....	....	...	...	...	...	....	...	....	...	...	...	.....
4/ 4/53	5	....	....	..	...	49,000	....	....	...	...	...	...	....	...	....	...	...	...	.....
4/ 6/53	..	....	....	..	...	28,400	....	....	...	...	...	...	....	...	....	...	...	...	.....
4/ 7/53	5	....	....	..	...	30,000	....	....	...	...	...	...	....	...	....	...	...	...	.....
4/ 8/53	..	....	....	..	...	19,100	....	....	...	...	...	...	....	...	....	...	...	...	.....
4/ 9/53	2	4.37	12.3	43	5.6	18,200	15.5	39.5	2.5	2.5	2.5	0.5	4.5	12.5	14.5	...	0.5	...	253,000
4/11/53	..	....	....	..	...	14,300	....	....	...	...	...	...	....	...	....	...	...	...	.....
4/13/53	2	....	....	..	...	16,500	....	....	...	...	...	...	....	...	....	...	...	...	.....
4/14/53	2	....	....	..	...	13,200	....	....	...	...	...	...	....	...	....	...	...	...	.....
4/15/53	2	....	....	..	...	14,000	....	....	...	...	...	...	....	...	....	...	...	...	.....
4/16/53	..	4.33	12.8	43	5.5	9,200	12.0	35.5	5.5	4.5	2.0	1.0	3.0	8.5	26	0.5	1.5	...	242,000
4/18/53	3	....	....	..	...	14,500	....	....	...	...	...	...	....	...	....	...	...	...	.....
4/20/53	..	....	....	..	...	10,200	....	....	...	...	...	...	....	...	....	...	...	...	.....
4/21/53	3	....	....	..	...	13,600	....	....	...	...	...	...	....	...	....	...	...	...	.....
4/22/53	3	....	....	..	...	13,200	....	....	...	...	...	...	....	...	....	...	...	...	.....
4/23/53	3	4.53	13.4	46	4.0	13,000	15.0	34	2.0	4.0	5.0	1.5	1.5	5.0	30.5	0.5	...	1.0	240,000
4/24/53	..	....	....	..	...	13,500	....	....	...	...	...	...	....	...	....	...	...	...	.....

* Bone marrow findings on April 2, 1953: neutrophiles 66.2% (segmented 25.4%, bands 29.4%, juveniles 11.4%); myelocytes 11.0% (neutrophiles 9.6%, eosinophiles 1.4%); promyelocytes 0.4%, blast forms 0.8%, lymphocytes 1.0%, monocytes 0.4%, eosinophiles 3.6%, basophiles 0.2%, histiocytes 0.2%, normoblasts 15.0%, erythroblasts 1.2%; erythroid-myeloid ratio 1 to 5.2; megakaryocytes present. This bone marrow is compatible with that of myelogenous leukemia.

triglutamate (Teropterin), triethylene melamine twice, x-ray to spleen three times, radioactive gold intravenously, large doses of specially prepared yeast (Merck), and corticotropin (ACTH), none of which produced either a striking reduction in size of the large spleen or a satisfactory hematological remission. On Feb. 12, 1953, when the white cell count was 125,000, the patient was given two doses of triethylene thiophosphoramide at another institution, 5 mg. on Feb. 12 and 10 mg. on Feb. 19 intramuscularly. When the white cell count rose to 150,000, x-ray to the spleen was again administered, 250 r from Feb. 27 to March 4; this treatment, however, failed to reduce the white cell count and triethylene thiophosphoramide was again started. From March 19 to March 26 the patient received 70 mg. of triethylene thiophosphoramide intramuscularly. The white cell count was reduced to 100,000 on March 26, 1953.

On April 2, 1953, the patient was referred to us for review and consideration for further use of triethylene thiophosphoramide. The spleen in the nipple line measured 7 cm. above the costal margin and 15 cm. below it, while the lower border of the liver was palpable 5.5 cm. below the costal margin and the upper border of liver dullness extended to 10 cm. above this margin. Table 4 gives the dosage of drug, avenue of administration, and blood cell counts. The change

in blood cell count was accompanied by a striking reduction in size of liver and spleen within three weeks of treatment and after only 38 mg. of triethylene thiophosphoramide intravenously. In addition to the very satisfactory hematological response, the patient feels clinically well, his appetite is good, and he has gained 3 lb. (1.3 kg.) in the three weeks since starting on his present course of triethylene thiophosphoramide. At this time, his spleen measured 6.5 cm. above and below the costal margin in the nipple line. It is especially interesting to note that after the second intravenous dose of the drug the patient volunteered the information that the tension and pressure in his abdomen was noticably reduced.

Hodgkin's Disease.—N. W. is a 20-year-old girl for whom the diagnosis of Hodgkin's disease was made from a lymph node biopsy about a year previous to her present admission to the

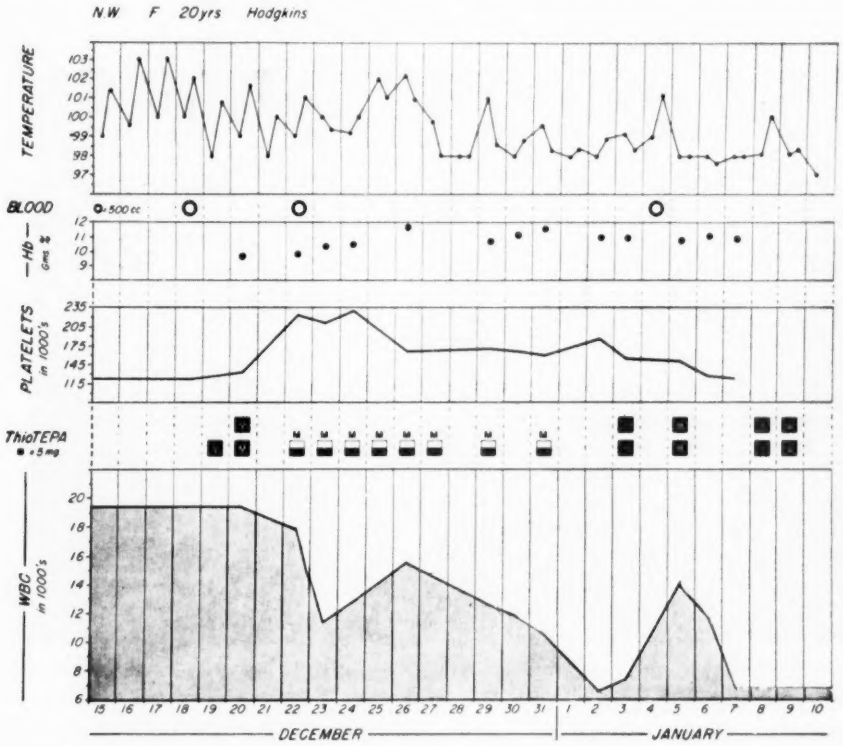

Fig. 6.—Hematologic and temperature response to triethylene thiophosphoramide in a patient with Hodgkin's disease previously treated twice with x-ray.

Northern Division of the Einstein Medical Center. X-ray therapy had induced two remissions, the last one in October 1952. In December a relapse occurred, ushered in with high fever, cough, malaise, weakness, and pain in the back. Moderate anemia and a leucocyte count of 20,000 per cubic millimeter were found at this time.

Treatment with triethylene thiophosphoramide, as indicated in Figure 6, was begun on Dec. 19, 1952. The back pain disappeared, the temperature returned to normal, the leucocyte count dropped to 8,500 cells per cubic millimeter, and there was general clinical improvement. Coincident with these changes, a decrease in the size of a retroperitoneal tumor mass as outlined by urography (Fig. 7) as well as of a mediastinal mass (Fig. 8) has occurred. As of April 19, 1953, the patient is in complete clinical remission and is receiving 5 to 10 mg. of triethylene thiophosphoramide intramuscularly every two weeks as a maintenance dose.

Lymphosarcoma.—Triethylene thiophosphoramide has been less effective in lymphosarcoma.

G. M., a 5-year-old boy, had an upper respiratory infection in early September 1952, from which he made an uneventful recovery. On Oct. 2, 1952, his mother noticed swelling on both sides of the neck and a cough developed. Pleural effusion appeared on the left side, and repeated thoracentesis became necessary. He was admitted to the hospital on Oct. 20, 1952. Bone marrow on aspiration showed extensive lymphomatous involvement interspersed with considerable normal marrow elements.

Large masses of enlarged anterior and posterior cervical lymph nodes were present. The left hemithorax appeared to be completely involved in an extensive effusion, and the mediastinum was shifted to the right. The spleen was palpable 6.0 cm. and the liver 1 cm. below the left and right costal margins, respectively. There was bilateral axillary and inguinal lymphadenopathy.

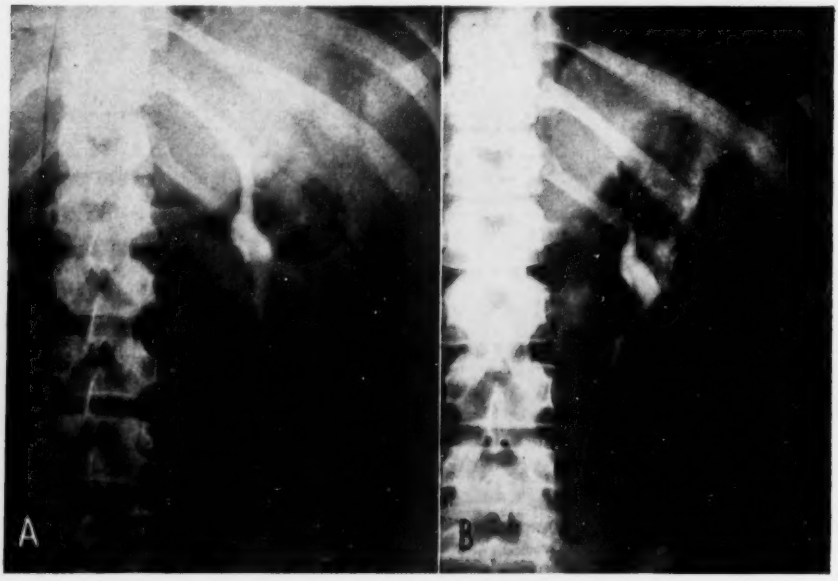

Fig. 7.—Intravenous urograms showing (*A*) displacement of upper portion of ureter by tumor mass and (*B*) disappearance of the mass after treatment.

At the time of admission, except for a severe cough and rapid respiration, the child had no specific complaints. On an x-ray film of the chest after thoracentesis, the mediastinum measured 10.5 cm. in width.

Triethylene thiophosphoramide was started on Nov. 1, 1952, and the hematological findings are shown in Figure 9 until Jan. 6, 1953.

Under treatment, the peripheral nodes underwent very marked regression. By Nov. 9, 1952, 18 days after treatment with triethylene thiophosphoramide was started, the child felt well; his cough, while still present, was less troublesome, and a remarkable decrease in the cervical adenopathy had occurred so that only a few remnants less than 0.5 cm. in diameter could be palpated, in comparison with nodes that had originally measured 2 by 2 by 2 cm. The spleen was palpable less than 1.0 cm. below the costal margin. However, because of the degree of depression of the peripheral white cell count we could not administer the drug as frequently as previously. Although the rate of accumulation of fluid in the left side of the thorax decreased, there was no appreciable decrease in the size of the mediastinal mass, and by Jan. 6, 1953, this mass appeared to be larger than previously. On Jan. 7, 1953, x-ray studies also showed a retro-

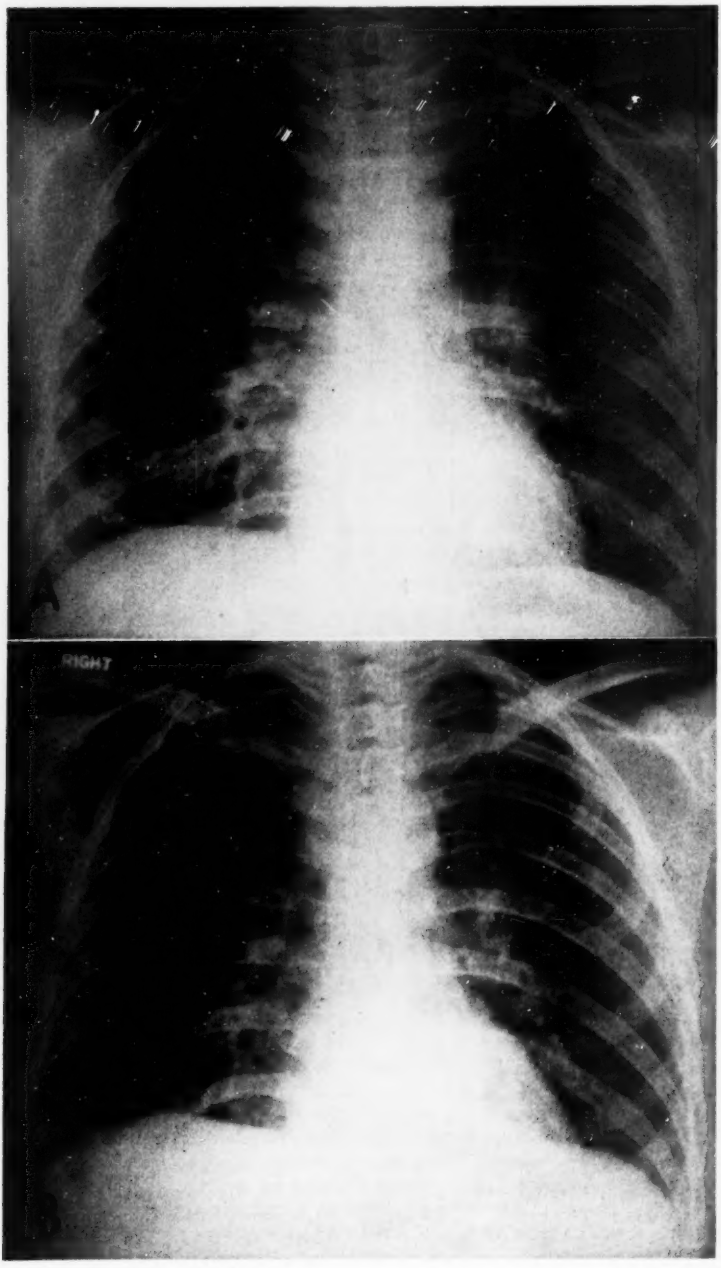

Fig. 8.—Chest x-ray (*A*) before and (*B*) four weeks after triethylene thiophosphoramide was started. Note change in mediastinal shadow.

pharyngeal mass as well as what appeared to be an abdominal mass behind the stomach. Local x-ray therapy was started at this time. While this produced a decrease in the masses noted, the patient continued a downhill course and died on Feb. 21, 1953, following the onset of an acute respiratory obstruction.

Acute Leukemia.—Results that have been almost completely discouraging have occurred in the treatment of the acute leukemias. These results are illustrated by the following case.

J. B., a boy aged 30 months, was in good health until Sept. 4, 1952, when his parents noticed the appearance of bruises which failed to clear. A diagnosis of leukemia was made from a blood

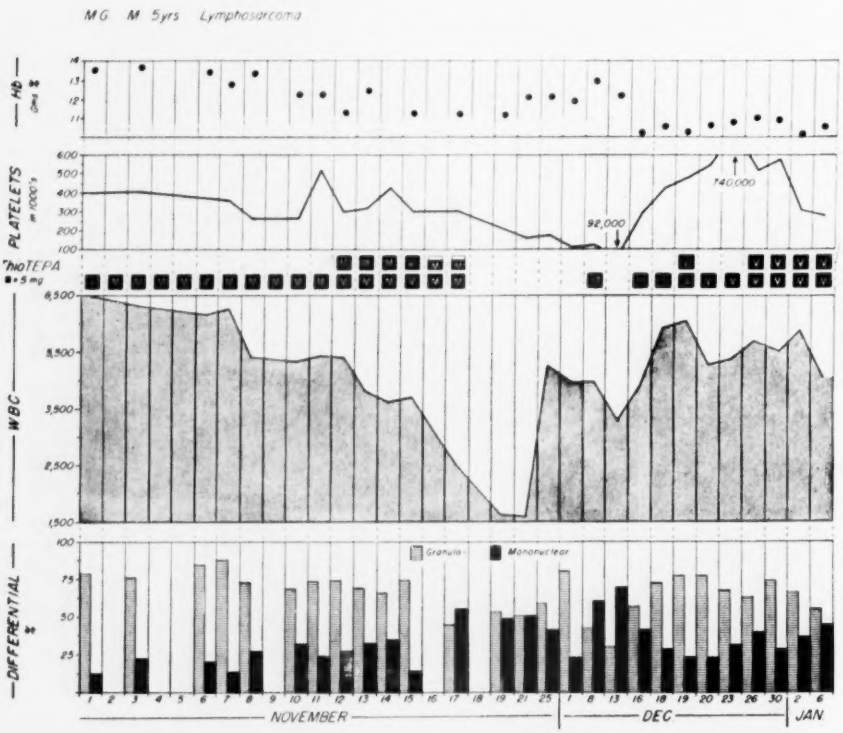

Fig. 9.—Hematologic response to triethylene thiophosphoramide in a patient with lymphosarcoma.

count at a Scranton Hospital. He was treated with cortisone, transfusions, and 4-aminopteroyl glutamic acid (Aminopterin) and was doing well until Oct. 15, when hematuria appeared and continued until Oct. 22. The child was listless and exhausted. On Oct. 24, an upper respiratory infection developed and was treated with oxygen, oxytetracycline (Terramycin), and penicillin. The patient received three more blood transfusions, of 250 cc. each, between Oct. 26 and Oct. 31. He appeared to improve and was discharged to his home on Nov. 4. On Nov. 13, he was readmitted to the Scranton Hospital with a high fever and was again treated with antibiotics and transfusions, and on Nov. 19 he was transferred to St. Christopher's Hospital.

On admission the child was pale, apprehensive, and sweating profusely. There was bilateral anterior and posterior cervical lymphadenopathy as well as enlargement of the axillary and inguinal lymph nodes. The liver edge was palpable 3.5 cm. and the spleen 12.0 cm. below the right and left costal margins, respectively. Many petechiae and ecchymotic areas were scattered

over the entire body and were especially marked over the lower extremities. The temperature was 101 F. Marrow aspiration and peripheral blood findings confirmed the diagnosis of an acute stem cell leukemia. Treatment with triethylene thiophosphoramide was begun on Nov. 15, and dosage as well as hematological findings are shown in Figure 10.

The patient seemed to improve somewhat clinically until Nov. 29, at which time his peripheral lymph nodes had decreased in size considerably and the spleen was palpable only 5 cm. below

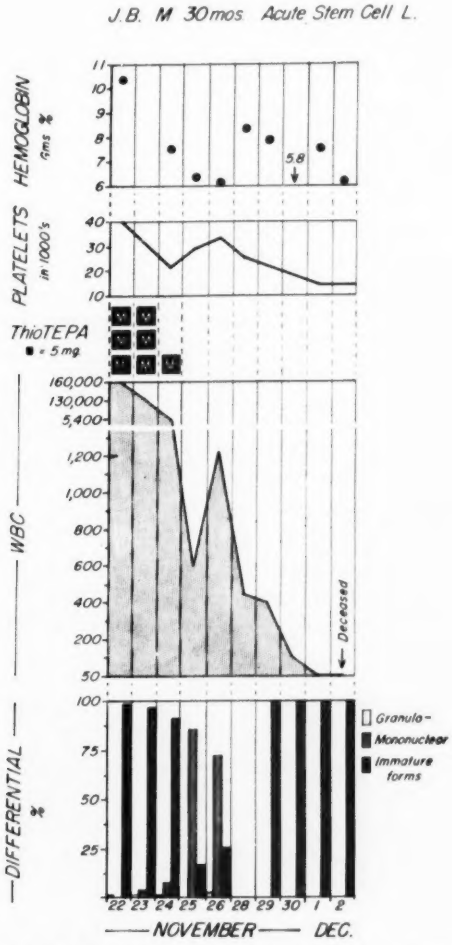

Fig. 10.—Failure of triethylene thiophosphoramide favorably to modify the course of acute leukemia.

the costal margin. The next day jaundice first became evident and tarry stools, which had occurred previously, increased in frequency. From this point, the course continued progressively downhill, and the child died on Dec. 2, 1952.

We know from repeated bone marrow studies in cases of acute stem cell leukemia that triethylene thiophosphoramide may rapidly eradicate the malignant bone marrow but in doing so leaves too little effective marrow to support the body's needs. If

measures can be devised to stimulate normal regeneration and at the same time more slowly destroy the malignant marrow tissue with carefully gauged doses of the drug given to these patients, perhaps some use for this drug in acute leukemias may be found. Such supplementary therapy has been tried with cortisone, without appreciable benefit to the patient.

Of the nonleukemic patients with inoperable malignant disease treated thus far, most have had such advanced metastatic disease that no alteration in the inexorable progress of the disease could possibly be expected. Of the 12 patients, however, 3 have shown what appears to be a slowing up of the course of the disease, and two of these have shown striking clinical and objective improvement. Both are patients who have had radical mastectomy for adenocarcinoma of the breast and have had recurrence in the scar, and adjacent skin seeding with metastatic axillary masses.

COMMENT

The clinical application of triethylene melamine by Karnofsky, Burchenal, Rhoads, and their associates,[8] following the discovery of its nitrogen-mustard-like effects on experimental tumors and leukemia in mice,[9] introduced an agent that was not only effective when given by mouth but also one that produced toxic manifestations of nausea and vomiting to a much less degree. Although the development of this compound involved perhaps no new principle of tumor chemotherapy, it did represent a significant advance in practical management. In view of the oncolytic action of triethylene melamine, other ethylenamine derivatives, including a number of phosphoramides, were prepared by the research staff of the Calco Chemical Division of the American Cynamid Company, among which the action of triethylene phosphoramide has been studied in a variety of mouse and rat tumors by Buckley and his associates [10] and by Sugiura and Stock [11] and results of its clinical application have been reported recently by Farber and his associates [12] and by Sykes, Karnofsky, Philips, and Burchenal.[13]

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8. Karnofsky, D. A.; Burchenal, J. H.; Armistead, H. C.; Southam, C. M.; Bernstein, J. L.; Craver, L. F., and Rhoads, C. P.: Triethylene Melamine in the Treatment of Neoplastic Disease: Compound with Nitrogen-Mustard-Like Activity Suitable for Oral and Intravenous Use, A. M. A. Arch. Int. Med. **87**:477, 1951.

9. Lewis, M. R., and Crossley, M. L.: Retardation of Tumor Growth in Mice by Oral Administration of Ethylenimine Derivatives, Arch. Biochem. **26**:319, 1950. Burchenal, J. H.; Crossley, M. L.; Stock, C. C., and Rhoads, C. P.: The Action of Certain Ethylenimine (Aziridine) Derivatives on Mouse Leukemia, ibid. **26**:321, 1950.

10. Buckley, S. M.; Stock, C. C.; Parker, R. P.; Crossley, M. L.;Kuh, E., and Saeger, D. R.: Inhibition Studies of Some Phosphoramides Against Sarcoma 180, Proc. Soc. Exper. Biol. & Med. **78**:299, 1951.

11. Sugiura, K., and Stock, C. C.: The Effect of Methylbis (β Chlorethyl) Amine Oxide, N,N′,N″,-triethylene Phosphoramide and N,N-diethyl-N′,N″-diethylene Phosphoramide on the Growth of a Variety of Mouse and Rat Tumors, Abstracted, Cancer Research **12**:300, 1952.

12. Farber, S.; Appleton, R.; Downing, V.; Heald, F.; King, J., and Toch, R.: Clinical Studies of the Carcinolytic Action of Triethylene Phosphoramide, Cancer **6**:135, 1953.

13. Sykes, M. P.; Karnofsky, D. A.; Philips, F. S., and Burchenal, J. H.: Clinical Studies on Triethylenephosphoramide and Diethylenephosphoramide: Compounds with Nitrogen Mustard-Like Activity, Cancer **6**:142, 1953.

The possible usefulness of the sulfur derivative, triethylene thiophosphoramide, was uncovered as described above, and we have recently reported its effects in both chronic and acute myelogenous leukemia in rats [14] when it is administered intravenously or by stomach catheter.

Since the activity of triethylene thiophosphoramide is dependent upon its contained ethylenimine residues, it was reasonable to assume that it might have rather marked cytotoxic and tumor inhibitory action in the animal, since it contains three such residues. Burchenal and his associates [15] and Hendry and his associates [16] have both stressed the importance of at least two ethylenimine residues in the molecule as a requisite for satisfactory oncolytic activity.

Hendry, Homer, Rose, and Walpole [16] from results obtained with ethylenimine derivatives attribute their cytotoxic action primarily to changes produced in the chromosomes and preferentially, if not exclusively, directed towards dividing cells. This action, however, is not restricted to malignant cells but extends to proliferating cells of all types. Karnofsky and his associates [17] from a study of the action of the standard nitrogen mustards upon tumors in mice and in tissue culture could find nothing to suggest that these substances had a substantially selective effect upon neoplastic cells, and Farber and his associates [12] have stressed bone marrow depression as the most significant toxic manifestation of triethylene phosphoramide. While depression of bone marrow may also be produced by triethylene thiophosphoramide, it is nevertheless possible to administer triethylene thiophosphoramide with safety to the patient if the dose employed is selected for the patient and is controlled by careful hematological studies, just as Farber and his associates [12] found to be true for triethylene phosphoramide. Furthermore, if undue bone marrow depression does become evident, such depression is readily reversed by withholding the drug (see Fig. 9, Nov. 16 to Nov. 25).

However, with respect to immediate toxicity after administration, which action, we believe to be of a different nature from that of depression of the bone marrow, triethylene thiophosphoramide is remarkable in that it has produced no nausea or vomiting, has caused no venous thrombosis when administered intravenously, and has not even caused local pain when injected intramuscularly.

Patients under treatment with triethylene thiophosphoramide, especially if the white blood cell count is very high, should be kept on a high fluid intake as well as on medication to maintain the reaction of the urine above pH 7.0. Rapid cytolysis in such patients may lead to the formation of uric acid urinary calculi, which can produce obstructive uropathy.

While triethylene thiophosphoramide differs from triethylene phosphoramide only in the replacement of a double bond oxygen atom in the molecule by a sulfur

14. Shay, H.; Gruenstein, M., and Atwater, J.: Study of Effects of Triethylenethiophosphoramide (Thio-TEPA) in 2 Varieties of Myelogenous Leukemia in Rats, abstracted, Proc. Am. Assoc. Cancer Research **1**:50, 1953.

15. Burchenal, J. N.; Johnston, S. F.; Crener, M. A.; Webber, L. F., and Stock, C. C.: Chemotherapy of Leukemia: V. Effects of 2,4,6-Triethylenimino-s-Triazine and Related Compounds on Transplanted Mouse Leukemia, Proc. Soc. Exper. Biol. & Med. **74**:708, 1950.

16. Hendry, J. A.; Homer, R. F.; Rose, F. L., and Walpole, A. L.: Cytotoxic Agents: III. Derivatives of Ethylenimine, Brit. J. Pharmacol. **6**:357, 1951.

17. Karnofsky, D. A.; Burchenal, J. H.; Ormshee, R. A.; Cornman, I., and Rhoads, C. P.: Approaches to Tumor Chemotherapy, American Association for the Advancement of Science, 1947, p. 293.

atom, this difference appears to contribute some change in action if we compare the sustained beneficial effects which triethylene thiophosphoramide has thus far maintained in the treatment of our patients with chronic leukemia with the very limited response of similar patients treated with triethylene phosphoramide.[18]

Equal in significance to the results which we have obtained in the treatment of the chronic leukemias with this compound has been the response in the two patients with recurrent and metastatic breast carcinoma following radical removal of the primary breast lesion. The disappearance of the metastatic axillary mass and the gradual sloughing and healing of the recurrent malignant lesions in the operative scar, complete in one and thus far partial in the other, has presented a striking therapeutic result. Here, too, however, we would emphasize that treatment has only lasted over a few months, and whether all malignant cells can be eliminated or held in check indefinitely still remains to be determined.

Clinical experience with the use of triethylene thiophosphoramide has been too short in time and the cases treated too few to permit any definitive statement as to its ultimate value at this time, but, from our experience thus far, we believe triethylene thiophosphoramide shows promise of being an important addition to the chemotherapy of leukemias and possibly of other neoplastic diseases.

SUMMARY

Since this preliminary report represents a clinical experience with the drug of only six months' duration, the following comments are presented merely as some of our impressions of the value of triethylene thiophosphoramide at this time. These are derived from the treatment of 49 patients, 39 with malignant disease originating in the hemopoietic system and 10 with other inoperable malignant lesions.

Triethylene thiophosphoramide is a suppressive drug effective in the control of the chronic leukemias but is not a cure.

Administered intravenously or intramuscularly in the dosages recorded, it is remarkably free of any immediate toxic effect, such as nausea, vomiting, or even local pain following injection. No local venous thrombosis has occurred from its administration intravenously.

Manifestations of the cytotoxic action of the drug are most striking in the acute leukemias. However, the rapid destruction of primitive leukemic elements has not been followed by any favorable response in the acute leukemias. Triethylene thiophosphoramide, therefore, does not appear to be of any value in the management of the acute leukemias.

The most gratifying results with this drug have been achieved in the chronic leukemias (myelogenous and lymphatic). Some patients apparently refractory to other forms of antileukemic therapy had satisfactory clinical and hematological remissions under triethylene thiophosphoramide therapy. These changes have been accompanied by surprising reductions in the size of very firm spleens, which did not occur with a symptomatic response in these patients obtained with other agents prior to the use of triethylene thiophosphoramide.

Since individual responses to the drug have varied, no fixed dosage schedule can be outlined at present. Best results have followed from daily administration of the

18. Farber and others.[12] Sykes and others.[13]

drug initially, guided by daily consideration of the hematologic picture. Subsequently, maintenance dosage must be established for each patient, and the frequency of blood counts can be reduced accordingly.

There appears to be a reasonable margin of safety between the "effective" therapeutic dose of the drug and that dose which will produce undue bone marrow depression.

Preliminary studies following the administration of the drug by stomach catheter have shown it to be effective in our chronic myelogenous leukemia in rats. The effectiveness of the drug clinically after oral administration is being studied. Of three patients who were shifted from parenteral therapy to oral administration, one with chronic lymphatic leukemia appears to continue to do well; two with chronic myelogenous leukemia are showing a good response, while patient P. H., with subacute myelogenous leukemia, did poorly on oral medication but again responded well to intramuscular injections.

The encouraging response of two patients with recurrent and metastatic adenocarcinoma of the breast would certainly warrant continued investigation of the possible action of triethylene thiophosphoramide in other patients with inoperable malignant lesions.

Since triethylene thiophosphoramide is only suppressive and not a cure, possible resistance to the drug which may develop in the malignant cell after prolonged therapy is yet to be determined.

PHENYLBUTAZONE

Further Clinical Evaluation

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THIS REPORT evaluates the use of phenylbutazone (Butazolidin) for 800 patients with a variety of diseases. It covers a period of 30 months, from November 1950 to May 1953. During the first eight months phenylbutazone was used with equal parts of aminopyrine as a mixture known in the United States as Butapyrin and in Europe as Irgapyrin. Phenylbutazone was first synthesized by H. Stenzl in the laboratories of the J. R. Geigy Company, Basle, Switzerland. The chemistry and pharmacology of this pyrazole have been reported elsewhere.[1]

Since numerous clinical reports have described the therapeutic benefits of Butapyrin in rheumatic diseases, it was felt desirable to evaluate the results of using phenylbutazone alone. At the request of the authors this compound was made available for clinical trials. After July 1951 phenylbutazone was used alone orally and intramuscularly. In previous communications [1] the therapeutic value and the toxicity of phenylbutazone and of Butapyrin in gout and various rheumatic diseases have been described. The present report is an expansion of our earlier investigation.

Dr. Windsor C. Cutting, Professor of Pharmacology and Therapeutics, gave advice.

This paper was presented before the American Rheumatism Association, New York, May 29, 1953.

From the Department of Pharmacology and Therapeutics, Rheumatic Disease Study Group, Stanford University School of Medicine.

The handling of our data was facilitated by the use of punched cards. Dr. L. E. Moses, of the Department of Statistics, helped us in the statistical treatment of the data.

Dr. Albert Hemming, of Geigy Pharmaceuticals, New York, gave advice during the course of this study, and Grants-in-aid were received from Geigy Pharmaceuticals, Division of Geigy Company, Inc.

1. (*a*) A review of the previous European literature is given in our first reference, in *The Journal of the American Medical Association*. Since the present report is essentially a statistical evaluation of our own experience, we have not referred to recent publications by others. Kuzell, W. C.; Schaffarzick, R. W.; Brown, B., and Mankle, E. A.: Phenylbutazone (Butazolidin) in Rheumatoid Arthritis and Gout, J. A. M. A. **149**:729, 1952. (*b*) Kuzell, W. C., and Schaffarzick, R. W.: Phenylbutazone (Butazolidin) and Butapyrin: Study of Clinical Effects in Arthritis and Gout, California Med. **77**:319, 1952; (*c*) Phenylbutazone (Butazolidin), Bull. Rheumat. Dis. **3**:23, 1952.

CLINICAL METHOD AND MATERIAL

Dosage of Phenylbutazone.—For the most part, phenylbutazone was administered orally in coated tablets containing 100 or 200 mg. or in capsules containing 200 mg. It was given intramuscularly in a 20% solution of the sodium salt alone or, because of pain at the site of injection, in combination with local anesthetics. The usual intramuscular dose was 1 gm.

In the early months of this study oral dosage ranged from 100 to 1,600 mg., but eventually the average daily dosage rarely exceeded 600 mg. The administration of phenylbutazone in gelatin capsules or in lightly to heavily coated tablets did not result in any appreciable difference in therapeutic benefit or toxic effect.

More rapid clinical improvement usually followed intramuscular rather than oral administration, despite the published reports indicating the more rapid rise of blood levels of phenylbutazone following oral administration.[2] Intramuscular administration was most commonly employed in treatment of acute gout and painful shoulder, in which cases daily injection of 1 gm. for one to three days was usually sufficient for relief of symptoms.

TABLE 1.—*Duration of Treatment with Phenylbutazone in 800 Patients*

	Patients, No. / Days, No.								
Disorder	800 and Over	700-799	600-699	500-599	400-499	300-399	200-299	100-199	99 and Under
Gout	0	3	5	9	13	9	15	24	121
Rheumatoid arthritis	3	6	8	5	11	15	14	15	86
R.A. of the spine *	0	2	1	4	3	4	6	6	25
R.A. with psoriasis	0	0	1	1	1	4	2	1	8
Painful shoulder	0	0	0	0	2	0	0	8	54
Osteoarthritis	0	0	0	0	5	3	5	15	88
Malum coxae senilis	0	0	0	0	2	0	2	2	1
R.A. with degenerative joint disease	0	1	0	2	4	3	4	9	42
Osteoporosis	0	0	0	0	0	0	1	4	17
Miscellaneous	0	1	0	0	0	0	5	3	86
Totals	3	13	15	21	41	38	54	87	528

Approximately 110,000 patient-days

* R.A. = rheumatoid arthritis.

Duration of Treatment with Phenylbutazone.—Eight hundred patients have been treated for approximately 110,000 patient-days. Inspection of Table 1 shows that 66% of the patients were treated for less than 100 days; the average was approximately 30 days. The remainder of the group were treated for periods ranging from 100 to 1,000 days. The most prolonged treatment was in cases of rheumatoid arthritis, ankylosing spondylitis, and chronic gout.

CLINICAL RESULTS

Gout.—Two hundred patients with gout were treated with phenylbutazone (Table 2). Major improvement was observed in 83%; in 14% there was minor improvement, and only 3% failed to respond. In no instance were signs and symptoms intensified. After intramuscular administration many patients experienced substantial relief of pain within the first hour. Forty-one percent of the gouty subjects were free of symptoms within 48 hours. With few exceptions patients found phenylbutazone more satisfactory than colchicine. A marked fall in values

2. Burns, J. J.; Schalert, A.; Chenkin, T.; Goldman, A., and Brodie, B.: The Physiological Disposition of Phenylbutazone (Butazolidin), A New Antirheumatic Agent, abstracted, J. Pharmacol. & Exper. Therap. **106**:375, 1952.

for serum uric acid followed use of the drug. These observations confirm our initial impression, first recorded in 1951,[3] that phenylbutazone exerts a specific effect in gout.

Rheumatoid Arthritis.—Phenylbutazone was administered to 163 patients with rheumatoid arthritis. The results were evaluated according to the criteria of the American Rheumatism Association[4] and are presented in Table 3. Among the 163 patients 96 (59%) enjoyed Grade I or II response. Forty patients (25%)

TABLE 2.—*Therapeutic Response of Gout to Phenylbutazone*

	Patients, No. Grades of Response †			
Stage *	I	II	III	IV
I	41	20	7	0
II	41	63	21	7
Totals	82	83	28	7

* Stage I. Acute gout, with asymptomatic periods between exacerbations. Stage II. Acute gout superimposed upon chronic gouty arthritis.

† Therapeutic response: Grade I. Complete remission in 48 hours or less. Grade II. Major improvement, indicating rapid decrease of signs and symptoms within 48 hours, but with slight persistence up to seven days following initial therapy. Grade III. Minor improvement with analgesia and decreased swelling but not complete remission, in spite of continued therapy. Grade IV. No effect.

TABLE 3.—*Therapeutic Response of Rheumatoid Arthritis to Phenylbutazone**

		Patients, No. Grade of Response				
Stage	Class	I	II	III	IV	Worse
I	I	1	4	6	1	..
	II	3	12	5	2	..
	III	..	1	..	..	..
	IV	..	1	..	..	..
II	I	..	..	..	1	..
	II	3	29	8	7	..
	III	1	13	3	2	..
	IV	..	1	..	..	..
III	II	1	5	1	1	..
	III	..	7	2	2	..
	IV	..	..	1	1	..
IV	II	1	4	4	3	1
	III	..	9	8	5	..
	IV	..	..	2	1	..
Totals		10	86	40	26	1

* Evaluation is in accordance with the criteria of the American Rheumatism Association.
Stage: Extent of rheumatoid progression; objective changes increasing from mild (I) to severe (IV).
Class: Functional capacity of the patient, ranging from complete activity (I) to incapacitation (IV).
Grade: Response of rheumatoid activity to therapy, ranging from complete remission (I) to complete lack of effect (IV).

experienced Grade III improvement, and 26 (16%) were not improved. The disease appeared to be intensified in one patient. As previously noted, upon discontinuation of medication symptoms returned within several days. Expansion of our series and prolongation of the period of observation has demonstrated that

3. Kuzell, W. C., and Schaffarzick, R. W.: Butapyrin in Acute Gout, abstracted, Stanford Med. Bull. **9**:195, 1951.

4. Steinbrocker, O.; Traeger, C. H., and Batterman, R. C.: Therapeutic Criteria in Rheumatoid Arthritis, J.A.M.A. **140**:659, 1949.

phenylbutazone is less beneficial in this disease than originally noted (59% Grade I or II improvement instead of 72% in the smaller initial series.[1a] An appreciable number of patients, nonetheless, enjoyed symptomatic relief depending on continuous medication.

Rheumatoid Arthritis of the Spine (Ankylosing Spondylitis).—Among 51 patients with ankylosing spondylitis (Table 4) 65% had a Grade I or II response.

TABLE 4.—*Therapeutic Response of Ankylosing Spondylitis to Phenylbutazone**

Stage	Class	Patients, No. Grades of Response I	II	III	IV
I	I	..	1	..	..
	II	..	1	..	..
II	II	4	8	5	3
	III	..	1	1	..
III	I	..	2	..	..
	II	..	2	2	1
	III	..	4	1	..
IV	II	..	4	1	1
	III	1	4	..	2
	IV	..	1	1	..
Totals		5	28	11	7

* For interpretation see footnote to Table 3.

TABLE 5.—*Therapeutic Response of Psoriasis with Arthritis to Phenylbutazone**

Stage	Class	Patients, No. Grade of Response I	II	III	IV
I	I	..	2	..	1
	II	..	1	..	1
II	II	..	3	3	..
	III	1	2	..	..
III	II	..	..	1	..
	III	..	1	..	..
	IV	..	1	..	..
IV	II	..	1	..	..
	III	..	..	1	..
Totals		1	11	5	1

* For interpretation see footnote to Table 3.

Twenty-two per cent derived minor improvement, and 13% showed no effect. In cases in which comparison with x-ray therapy was possible, phenylbutazone afforded greater improvement in 20, x-ray was better in 7, and results were equivocal in 1. In 15 patients the drug effected such a degree of improvement that x-ray therapy was not employed. Where comparison could be made with cortisone or hydrocortisone, five patients were better on steroid therapy and five were better on the pyrazole.

Rheumatoid Arthritis with Psoriasis.—Eighteen patients suffering from psoriasis and associated arthritis were treated with phenylbutazone (Table 5). Of

these patients 67% had a Grade I or II improvement, whereas 28% sustained minor improvement. In five patients with extensive psoriatic skin lesions there was cutaneous improvement.

Painful Shoulder.—This group comprised patients with peritendinitis, capsulitis, bursitis, and acute arthritis of the shoulder in whom the single presenting complaint was acute painful shoulder with limitation of motion. As indicated in Table 6, there were 64 patients in this category; major improvement was obtained in 67%, and 11% enjoyed minor improvement. No effect was found in 17%, and the condition was apparently worsened in 5%. The best results were obtained with parenteral administration in the early stages of the disorder. In the chronic cases the local injection of 37.5 to 50 mg. hydrocortisone in addition to the oral or

TABLE 6.—*Therapeutic Response of Painful Shoulder to Phenylbutazone**

	Patients, No. Grade of Response				
Stage	I	II	III	IV	Worse
Mild	3	5	1	3	..
Moderate	11	15	4	6	2
Severe	5	4	2	2	1
Totals	19	24	7	11	3

* Grade I. Complete remission of symptoms. Grade II. Major improvement. Grade III. Minor improvement. IV. No effect.

TABLE 7.—*Therapeutic Response of Osteoarthritis to Phenylbutazone**

	Patients, No. Grade of Response				
Stage	I	II	III	IV	Worse
Mild	5	10	4	6	1
Moderate	4	37	18	19	1
Severe	..	3	1	7	..
Totals	9	50	23	32	2

* For interpretation see footnote to Table 6.

parenteral administration of phenylbutazone gave better results than using either agent separately.

Osteoarthritis.—Table 7 shows the results of phenylbutazone therapy in 116 patients with osteoarthritis. Fifty-one percent experienced major symptomatic improvement. Twenty percent were given minor analgesia, while 28% were unimproved and 2% appeared to be worse.

Malum Coxae Senilis.—As may be observed in Table 8, good symptomatic relief was obtained in three of seven patients, whereas the others experienced a moderate degree of analgesia.

Rheumatoid Arthritis with Degenerative Joint Disease.—Sixty-five patients with "mixed arthritis" were treated with phenylbutazone, and the results are presented in Table 9. In this group only 39% showed Grade I or II improvement, while 28% are in Group III and 33% failed to respond.

Osteoporosis.—In 22 patients with postmenopausal senile osteoporosis (Table 10) major symptomatic improvement was gained in 45% when phenylbutazone

was administered together with androgenic and estrogenic hormones. Minor relief of pain appeared in 9%, and no effect was observed in 46%.

Miscellaneous Painful Disorders.—Phenylbutazone was evaluated regarding analgesia in a variety of other disorders (Table 11). One patient with rheumatic fever was given complete relief of joint pain while receiving phenylbutazone. There

TABLE 8.—*Therapeutic Response of Malum Coxae Senilis to Phenylbutazone**

	Patients, No. Grade of Response			
Stage	I	II	III	IV
Moderate	..	2	1	..
Severe	..	1	3	..
Totals	..	3	4	..

* For interpretation see footnote to Table 6.

TABLE 9.—*Therapeutic Response of Rheumatoid Arthritis with Degenerative Joint Disease (Mixed Arthritis) to Phenylbutazone*

		Patients, No. Grade of Response			
Stage	Class	I	II	III	IV
I	I	1	1	2	..
	II	..	1	..	1
II	I	..	2	..	..
	II	4	14	12	13
	III	..	..	2	2
III	II	..	..	2	3
	III	..	2	..	2
IV	III	..	..	..	1
Totals		5	20	18	22

* For interpretation see footnote to Table 3.

TABLE 10.—*Therapeutic Response of Osteoporosis to Phenylbutazone**

	Patients, No. Grade of Response			
Stage	I	II	III	IV
Mild	..	2	..	3
Moderate	1	7	2	3
Severe	..	..	..	4
Totals	1	9	2	10

* For interpretation see footnote to Table 6.

were 26 patients with fibrositis or myositis. Of these, six were completely relieved, two had major improvement, six had slight analgesia, and nine were not affected. Among eight patients with panniculitis three were slightly improved. There were seven patients with unclassified low back pain. Of these, three had disappearance of pain, and one was afforded major relief of pain. The remaining three were not affected. Eight patients with nerve root pressure (usually from herniated intervertebral disc) were treated with phenylbutazone. Three of these experienced

appreciable reduction in symptoms, and in the other four patients the pain was not modified. Among five patients with traumatic arthritis two were markedly improved and two others were given minimal relief. There were two patients with Sjögren's syndrome (keratoconjunctivitis sicca) and one of these experienced decreased arthralgia. There were three cases of lupus erythematosus, one of which was disseminated. In two of these cases there was a significant reduction in symptoms. In five patients with metastatic carcinoma relief of pain was complete in one, marked in another, and absent in three. One of three patients with migraine was given substantial relief. There was one patient with psoriasis treated with phenylbutazone, with diminution in the skin lesions. One of two patients with atopic dermatitis was observed to have clearing of skin lesions, while the other became worse. Two patients with bronchial asthma were unrelieved. One of four patients with mul-

TABLE 11.—*Therapeutic Response of Miscellaneous Painful Disorders to Phenylbutazone**

Disorder	Grade I	II	III	IV	Total
Rheumatic fever (arthralgia)	1	..	..	..	1
Fibrositis or myositis	6	5	6	9	26
Panniculitis	..	..	3	5	8
Low back pain	3	1	..	3	7
Nerve-root pressure (analgesia)	..	3	1	4	8
Traumatic arthritis	..	2	2	1	5
Sjögren's syndrome	..	1	..	1	2
Lupus erythematosus	..	2	..	1	3
Metastatic carcinoma (analgesia)	1	1	..	3	5
Migraine	..	1	..	2	3
Psoriasis (dermatitis)	1	..	..	..	1
Atopic dermatitis	..	1	..	1	2
Bronchial asthma	..	..	..	2	2
Multiple sclerosis	..	..	1	3	4
Parkinsonism (tremor)	..	..	..	2	2
Miscellaneous painful disorders	3	1	2	3	9
Edema of macule	1	..	..	..	1
Scalenus anticus syndrome	..	1	..	..	1
Peripheral vascular disease	..	..	2	2	4
Totals	16	19	17	42	94

* Grade I. Complete symptomatic relief. Grade II. Major symptomatic relief. Grade III. Minor symptomatic relief. Grade IV. No relief of symptoms.

tiple sclerosis showed slight improvement in symptoms while taking this medication, but the natural course of this disease makes evaluation precarious. There was no effect in the tremor of two patients with Parkinsonism. One patient with scalenus anticus syndrome had substantial relief of pain. One patient with idiopathic edema of the macule was improved following the use of phenylbutazone. Two of four patients with peripheral vascular disease were afforded slight reduction in pain. In nine other patients with miscellaneous painful conditions complete analgesia was given to three, nearly complete relief to one, minor relief to two, and no benefit to three.

TOXICITY

Among the 800 patients studied 321 (40%) showed untoward side-effects which in 121 (15%) instances were severe enough to warrant discontinuance of the medication. Table 12 shows the distribution of these side-effects among the patients with respect to diseases treated. There was in many instances more than one toxic

TABLE 12.—*Toxic Manifestations of Phenylbutazone*

Disorder	Total Patients Treated	Patients, No.																												
		Manifestations																												
		Water Retention	Hypertension	Cardiac Arrhythmia	Rash	Stomatitis	Epigastric Pain	Ulcer Activation	Constipation	Diarrhea	Nausea	G.I. Hemorrhage	Hepatitis	Vertigo	Lethargy	C.N.S. Stimulation	Visual Symptoms	Fever	Anemia	Leucopenia	Agranulocytosis	Thrombocytopenia	Purpura	Toxicity, No. Patients Showing	Drugs Discontinued Due to Toxicity
Gout	200	19	3	..	6	2	7	..	..	..	16	..	1	6	1	3	4	..	1	1	..	..	1	52	14
Rheumatoid arthritis	163	25	..	..	14	9	10	1	2	1	30	1	1	2	3	5	6	..	8	3	1	1	..	82	25
Ankylosing spondylitis	51	4	..	..	1	1	2	1	1	..	7	..	..	4	..	3	..	..	2	3	1	..	..	17	7
Psoriasis with arthritis	18	3	1	..	..	1	1	1	1	..	2	..	..	..	..	..	..	..	1	..	..	..	..	9	2
Painful shoulder	64	9	2	..	8	..	4	3	..	..	7	1	..	4	1	..	2	..	..	1	..	..	1	26	13
Osteoarthritis	116	15	3	..	5	2	4	1	1	2	17	..	..	6	3	2	1	..	..	1	1	..	1	48	20
Mixed arthritis	65	16	1	..	3	3	..	..	..	1	6	..	..	3	..	1	1	1	2	5	1	..	1	38	19
Osteoporosis	22	7	1	..	1	1	..	..	..	1	2	..	..	1	1	..	..	..	..	..	..	..	..	9	5
Malum coxae senilis	7	2	..	..	..	..	1	1	..	..	1	1	..	1	..	1	..	..	..	..	..	..	..	5	1
Miscellaneous	94	9	..	1	6	2	2	..	2	..	13	..	..	3	..	2	2	..	..	3	1	..	..	35	15
Totals	800	109	11	1	44	21	31	8	7	5	101	3	2	30	9	17	16	1	14	17	5	1	4	321	121

side-effect in individual patients; the 321 patients showed 457 toxic manifestations. We found 22 different side-effects. These were as follows: water retention, hypertension, cardiac arrhythmia, rash, stomatitis, epigastric pain, ulcer activation, constipation, diarrhea, nausea, gastrointestinal hemorrhage, hepatitis, vertigo, lethargy, central nervous system stimulation, visual symptoms, fever, anemia, leucopenia, agranulocytosis, thrombocytopenia, and purpura.

Of the 800 patients 145 received Butapyrin (18%); 523 received phenylbutazone (66%), and 132 received both Butapyrin and phenylbutazone (16%). Of those patients who received only Butapyrin 31 were unable to tolerate the medication (21%); of those who received only phenylbutazone 73 were unable to tolerate the medication (14%), and of those who received both Butapyrin and phenylbutazone 18 were unable to tolerate the medication (14%). While these data seem to indicate that phenylbutazone is less toxic than Butapyrin, it is pointed out that the latter medication was used in larger daily doses (the average was 750 to 1,500 mg.) in the initial phases of this investigation. Since, however, previous comparison of phenylbutazone with Butapyrin [1b] revealed no significant difference in therapeutic response, it appears that there is no advantage to be gained by giving aminopyrin with phenylbutazone.

Toxic Manifestations

Water Retention.—Of the individual toxic manifestations, water retention was most frequently encountered (14% of all cases). In most instances this was not a serious complication and was readily controlled by sodium restriction and reduction in the dose of phenylbutazone. Mercurial diuretic agents were ineffective in this type of water retention. In two elderly female patients frank cardiac decompensation occurred; both patients responded readily to digitalization. Hypertension appeared in 1.3% of patients receiving phenylbutazone. Auricular fibrillation was observed in one patient with "mixed arthritis" and rheumatic heart disease. Normal rhythm was restored upon discontinuance of the drug.

Rash.—Rash occurred in 5.6% of the patients treated in this series. In most instances the cutaneous manifestations were nonpruritic macular lesions which faded readily. There were, however, two cases of erythema multiforme bullosum, which healed uneventfully in three weeks. Generally there was a tendency for the rash to be more florid in the areas exposed to the sunlight. Of the 45 patients in whom drug rash from phenylbutazone developed 11 gave a history of previous drug sensitivity (24%). In 22 of these patients (44%) it was possible to resume or continue medication without recurrence or persistence of rash. In three others (6%) it was impossible to resume phenylbutazone therapy without recurrence of rash.

Stomatitis.—In 21 patients (2.6%) aphthous stomatitis of variable severity developed. These patients all gave a past history of similar episodes. This stomatitis was not accompanied by leucopenia. It was our impression that the administration of pyridoxine relieved the lesions.

Epigastric Pain.—Epigastric pain occurred in 34 of the 800 patients. This pain was unrelieved by antacids and antispasmodics, but it disappeared within several days after the cessation of phenylbutazone administration. In 20 of these patients the medication was discontinued. In eight epigastric pain developed while they were receiving parenteral medication.

Ulcer Activation.—There were eight instances of duodenal ulcer activation, an incidence of 1%. Five of these occurred in patients who had previously had peptic ulcer.

Disturbance in Bowel Habits.—The incidence of bowel disturbances was remarkably low. Seven patients complained of constipation and five of diarrhea, which symptoms disappeared on cessation of medication.

Nausea.—Nausea occurred in 101 patients (12.5%). Phenylbutazone was discontinued in 46 patients, among whom 19 had concomitant toxic manifestations. Often it was possible to ameliorate nausea with antacids or antispasmodics. Nausea was observed following both oral and intramuscular administration of phenylbutazone.

Gastrointestinal Hemorrhage.—Among the 800 patients there were 3 who had bleeding from the alimentary canal. One of these, a known bleeder, had bleeding from the gums following the intramuscular use of Butapyrin. Two men in the seventh decade had massive hemorrhage from duodenal ulcers. For one of these there was a history of bleeding ulcer. It is interesting that this patient received only intramuscular Butapyrin. The other patient bled while receiving phenylbutazone by mouth.

Hepatitis.—Two cases of toxic hepatitis were encountered during the course of pyrazole therapy. The first of these was of a 66-year-old woman with severe rheumatoid arthritis, who had a history of radical mastectomy for carcinoma and who had been given a transfusion of 1 liter of whole blood immediately prior to treatment with Butapyrin. After four weeks of oral medication marked jaundice developed, from which she recovered uneventfully. Since she lived in a distant community, we were unable to make liver function tests. In this case the hepatitis cannot be definitely attributed to phenylbutazone. The other case occurred in a 55-year-old man with gout, who had had ulcerative colitis and hypertensive cardiovascular disease and who had recently passed a renal calculus. He had received several injections of penicillin several weeks prior to the onset of icterus. This man had been taking phenylbutazone orally for two weeks when indigestion and jaundice developed. The liver was slightly tender but not greatly enlarged. The icterus index was 64, and the cephalin flocculation test was 4+. Following discontinuance of medication, recovery was uneventful.

Vertigo.—This side-reaction occurred to a variable degree in 30 patients (3.7%), but in only two cases was it of sufficient degree to necessitate the discontinuance of medication.

Lethargy.—Lethargy was reported by nine patients (1%).

Central Nervous System Stimulation.—Evidences of stimulation of the central nervous system appeared in 16 patients. These ranged from simple loquaciousness and insomnia to frank psychosis with hallucinations in two patients (0.25%). Among the patients in this group nine had previous signs of disturbance of the central nervous system, including psychoneurosis, Parkinsonism and multiple sclerosis.

Visual Symptoms.—Fourteen patients complained of visual disturbance, which they variously described as blurring, flickering, or focusing difficulty. In all but one case the symptoms were transitory. This patient had for some time previously

been under the care of an ophthalmologist, who was treating her for amblyopia, imbalance of the extraocular muscles, and narrowing of the visual fields. She had a strongly positive Wassermann and Kolmer reaction in the cerebrospinal fluid. Her symptoms lessened while continuing treatment with phenylbutazone. In three other patients in this group there was preexisting iridocyclitis, and in another patient diabetes, hypertension, and residual cerebral hemorrhage were coexistent.

Fever.—While one patient was taking phenylbutazone a fever developed for which no other explanation could be found than drug reaction.

Anemia.—Thirteen patients became more anemic while taking phenylbutazone. Eight of these had rheumatoid arthritis of Stage III or IV, Class III or IV. The drug was continued in six of these together with hematinics, and transfusions of whole blood were given to three. Two patients with mixed arthritis, one with psoriasis with arthritis and two with ankylosing spondylitis, became anemic, and in all but one the drug was continued. Among the 13 patients with anemia only 2 were males, and one of these, a radiologist, also had ankylosing spondylitis and monocytic leukemia. In him an acute aplastic anemia developed, which responded favorably to multiple transfusions of whole blood and red cells.

Often within the first few days of therapy, hemodilution, due to fluid retention, gave an apparent anemia which was of no consequence.

Leucopenia.—In 17 patients (2.1%), of whom 14 were females, leucopenia developed. The drug was discontinued for 10 of these. The others, after discontinuing its use for several days, were able to continue the medication at a lower dosage. Two of these patients also were counted in the "anemia" section above. Six of these patients had a history of toxic manifestations associated with the use of other drugs. Leucopenia developed in three of these patients while they were concurrently receiving roentgen therapy and phenylbutazone. Five of them were concurrently receiving hydrocortisone intra-articularly.

Thrombocytopenic Purpura.—An aged woman with mixed arthritis had been treated with weekly doses of gold for two years in a neighboring university hospital, and thrombocytopenic purpura developed after administration of phenylbutazone. After a period of recovery, we again cautiously tried phenylbutazone in small doses orally and parenterally and the thrombocytopenia reappeared. The thrombocytopenia disappeared completely on final discontinuance of the medication.

Purpura.—There were four cases of purpura without thrombocytopenia in females, one of whom also was classified in the "anemia" section above.

Agranulocytosis.—Five cases of agranulocytosis were observed. One of the patients received Butapyrin, and agranulocytosis developed in the others while they were taking phenylbutazone. Brief case histories of these patients follow.

CASE 1.—A 67-year-old housewife with moderately severe osteoarthritis had been taking phenylbutazone 200 mg. twice daily for two months. There was no past history of drug sensitivity, and she was taking no other potentially sensitizing medication. On May 23, 1952, a sore throat, chills, fever, weakness, and headache developed. When she first reported to us, on May 26, the pharynx was hyperemic, there was no lymphadenopathy, and the temperature was 38.3 C. The leucocyte count was 1,400, with 8% polymorphonuclear cells. Phenylbutazone was discontinued, and the patient was hospitalized. Treatment included penicillin procaine, chlortetracycline (aureomycin), methionine, and multiple hematinics. Throat culture yielded Staphylococcus aureus (coagulase positive) and hemolytic Streptococcus. By the second hospital day the patient was afebrile and the pharynx was less red. The leucocyte count was 2,100, with 10% polymor-

phonuclear cells. Clinically the patient continued to improve rapidly, and on the sixth hospital day the white blood cell count rose to 5,500, with 71% polymorphonuclear cells. Use of phenylbutazone was not resumed in this case.

CASE 2.—A 36-year-old woman stenographer with severe rheumatoid arthritis (Stage IV, Class III) started taking Butapyrin on March 1, 1951. In the past she had had a gold dermatitis in the ears. The dosage ranged from 750 mg. to 1,500 mg. daily, orally or intramuscularly. The patient sustained an excellent response (Grade II). On Sept. 14, 1951, medication was changed from Butapyrin to phenylbutazone, 400 to 800 mg. daily by mouth, with an occasional intramuscular injection of 1.0 gm. On July 3, 1952, while on a trip, the patient had a sore throat and fever, for which a doctor in another community gave her penicillin by mouth. When next seen by us, on July 6, 1952, the patient's temperature was 37.4 C. (99.4 F.), her tonsils were covered with a white membrane, and she appeared quite toxic. Phenylbutazone was discontinued, and she was admitted to the hospital, where the leucocyte count was found to be 4,800, with 47% polymorphonuclear cells. Throat culture yielded Proteus vulgaris. Treatment included penicillin, oxytetracycline, methionine, and multiple hematinics. On July 7 the leucocyte count was 2,020, with 1% polymorphonuclear cells. The patient continued to have septic fever, and daily blood counts showed no change. On July 9 treatment with cortisone, 25 mg. four times daily, was begun. By July 11 the leucocyte count had risen to 7,750, with 31% polymorphonuclear cells and the patient was afebrile, with the pharynx clear. At this time there was exacerbation of the arthritic symptoms, which were reasonably well controlled by cortisone. Hematologic recovery was complete. On Sept. 13, 1952, because of recrudescence of joint symptoms, the patient was given phenylbutazone, 1.0 gm. intramuscularly, and subsequently she has received the compound orally and intramuscularly without recurrence of leucopenia.

CASE 3.—A 57-year-old stenographer with severe rheumatoid arthritis (Stage IV, Class II) had taken phenylbutazone orally and intramuscularly since Dec. 21, 1951. The average daily dose was 600 mg. Since Dec. 28, 1951, she had also taken acetosulfone, (sodium 2-N-acetylsulfamyl-4,4'-diaminodiphenyl sulfone), 1.0 gm. daily. In 1942 she had experienced a gold rash. On Jan. 18, 1952, she reported malaise and symptoms of a mild upper repiratory infection. The leucocyte count on this date was 4,800, compared with a recent count of 12,600, and at the same time hemoglobin had fallen from 13.6 gm. to 9.8 gm. Use of phenylbutazone and acetosulfone was discontinued. By Jan. 21, the patient had only symptoms referable to the arthropathy but the temperature was 37.2 C. (99 F.). On this date the white blood cell count was 1,900, with 30% polymorphonuclear cells, and the hemoglobin was 10.9 gm. Treatment included penicillin, multiple hematinics, cortisone, and transfusion of 500 cc. of whole blood. On Jan. 23 the leucocyte count was 1,800, with 13% polymorphonuclear cells, and the hemoglobin was 11.2 gm. Daily blood cell counts remained within this range until Feb. 2, when the white blood cell count rose to 4,700, with 26% polymorphonuclear cells, and the hemoglobin to 14.4 gm. Following this hematologic recovery proceeded rapidly to completion. On Feb. 4, 1952, phenylbutazone was resumed by injection and then by mouth with no depression in any phase of the patient's blood elements.

CASE 4.—A 49-year-old woman with mild rheumatoid arthritis (Grade II, Class II) had been taking phenylbutazone orally and occasionally intramuscularly since Dec. 10, 1951. The average daily dose was 600 mg. She also was taking acetosulfone and androstenediol. On Jan. 28, 1952, symptoms of an upper respiratory infection with a low-grade fever, 37.2 C. (99 F.), developed. Blood studies on Jan. 29 revealed hemoglobin 10.9 gm. and 2,080 white blood cells, with 6% polymorphonuclear cells. All the current medications were discontinued, and the patient was given penicillin and multiple hematinics. On Jan. 30 the hemoglobin was 10.9 gm. and leucocyte count was 3,000, with 27% polymorphonuclear cells. Clinical and hematologic improvement continued rapidly; on Feb. 4, the hemoglobin was 11.6 gm. and the white blood cell count was 4,600, with 69% polymorphonuclear cells. On March 21, 1952, phenylbutazone was resumed in an oral dose of 400 mg. daily, and subsequently the patient received several doses intramuscularly. At no time was there recurrence of leucopenia.

CASE 5.—A 63-year-old banker with moderately severe osteoarthritis had been taking Butapyrin, 500 mg. daily by mouth, since March 8, 1951. On May 31, 1951, a routine blood cell count revealed a depression of white blood cells, to 1,700, with 8% polymorphonuclear cells. The drug was discontinued, and the patient was given penicillin and cortisone. By June 4 the

leucocyte count was 1,330, with no polymorphonuclear cells, and the temperature was 37.8 C. (100 F.), but the patient felt perfectly well and examination revealed no focus of infection. At this time he was admitted to the hospital, where additional treatment included methionine, liver extract, and a course of corticotropin. One punctate aphthous ulcer developed and disappeared. It was not until June 13 that the first returning granulocyte appeared in the peripheral blood

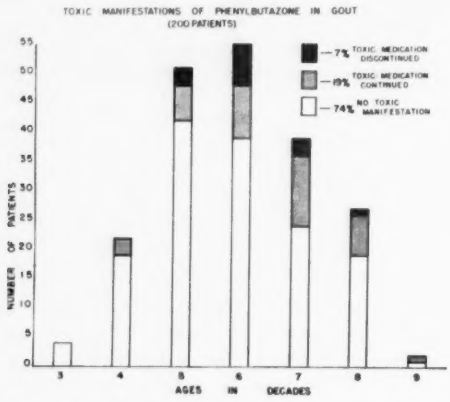

Chart 1.—Toxic manifestations of phenylbutazone therapy in gout (200 patients).

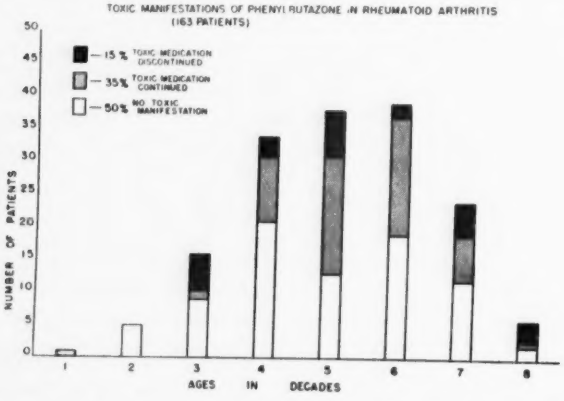

Chart 2.—Toxic manifestations of phenylbutazone therapy in rheumatoid arthritis (163 patients).

smear. From that date the blood picture improved, and by June 20 the leucocyte count was 9,400, with 51% polymorphonuclear cells. Pyrazole therapy has not been resumed in this case.

It is interesting that treatment with phenylbutazone was resumed in three (Cases 2, 3, and 4) of these cases following recovery from agranulocytosis and has been administered without untoward reaction to the date of this writing. It is of interest also that four of the five patients were women. Two of them were receiving acetosulfone at the same time. Three were also receiving barbiturates. One was receiving propylthiouracil.

Association of Toxicity With Age, Sex, Dosage, and Disease Treated

As may be observed upon inspection of Charts 1 to 4, there appears to be a difference in vulnerability to toxicity depending upon the disease. In gout, for example, in which therapeutic response was greatest, the incidence and severity of toxic manifestations were the least. In mixed rheumatoid and osteoarthritis, in which phenylbutazone therapy was least rewarding, the incidence and severity of untoward reactions were the greatest. As may be seen in Charts 1 to 4, age of the patient does not appear to influence the occurrence of toxicity significantly. The

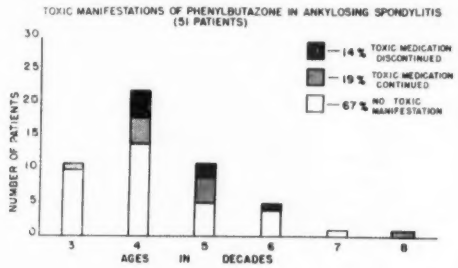

Chart 3.—Toxic manifestations of phenylbutazone therapy in ankylosing spondylitis (51 patients).

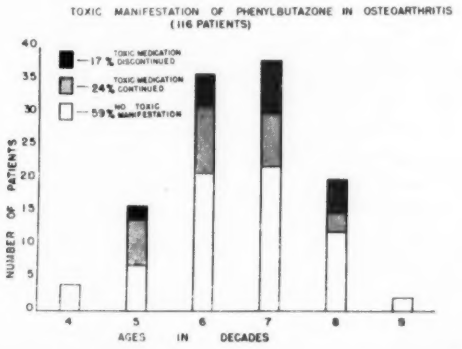

Chart 4.—Toxic manifestations of phenylbutazone therapy in osteoarthritis (116 patients).

incidence of untoward reactions was found to be generally greater in females than in males. In fact, 43% of females and 29% of males experienced toxic reactions, necessitating discontinuance of medication in 18% of females and 12% of males. In the entire group there were 471 females and 329 males. As might be expected, toxicity was demonstrated to be a function of dosage. When, in the early stages of this study, we often employed doses up to 1,600 mg. daily, we encountered appreciably more difficulty than when we adopted the policy of not exceeding 600 mg. daily.

In many instances patients with chronic gouty arthritis and ankylosing spondylitis required only 100 to 200 mg. of phenylbutazone daily. Administration of oral

dosage beyond 800 mg. per day appeared to increase the incidence of side-reactions without increasing therapeutic response. Above this level the incidence of toxicity rose from 32% at 800 mg. to 50% at 1,200 mg.

In Chart 5 the relative frequency of the various toxic manifestations is presented graphically. This shows that water retention and nausea are the most frequent toxic side-reactions, and it is interesting that among the 109 patients with water retention only 19 also had nausea although there were 101 instances of nausea.

When we attempted to relate the beneficial therapeutic response to the percent of patients in each disease group in which the phenylbutazone had to be discontinued due to toxic reactions, an interesting relationship became apparent. In Chart 6 it will be noted that the ratio of the percent of therapeutic benefit to percent of discontinuance due to toxicity is greatest in gout and least in "mixed arthritis."

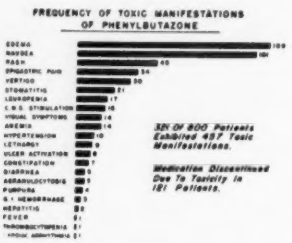

Chart 5.—Frequency of toxic manifestations of phenylbutazone therapy.

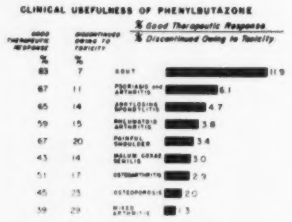

Chart 6.—Clinical usefulness of phenylbutazone.

This relationship shows a ratio of descending importance in the following order: gout, psoriasis with arthritis, ankylosing spondylitis, rheumatoid arthritis, painful shoulder, malum coxae senilis, osteoarthritis, osteoporosis, and mixed arthritis. Since the beneficial effect of phenylbutazone followed the same order, perhaps there is a true inverse relationship between the therapeutic benefit and the number of side-reactions in each disease group.

Effect of Mode of Administration on Toxicity and Therapeutic Response

Eighty-nine of the 800 patients received phenylbutazone only intramuscularly. Thirty-four percent of these patients showed toxic side-reactions due to phenylbutazone, and the medication was discontinued in 24% owing to toxicity. Parenteral administration oftentimes was quite beneficial in patients who had experienced only fair or poor symptomatic relief on oral medication. The reverse situation did

not obtain. The rapidity of response was also greater with intramuscular medication. Intramuscular administration was, however, sometimes limited by the provocation of local inflammatory reaction in the muscle. This painful inflammatory response was less frequent with phenylbutazone than with Butapyrin.

Concurrent Use of Gold and Cortisone

Sixty-six patients received aurothioglucose (Solganol-B) together with phenylbutazone, and the incidence of toxic manifestations was not increased. Likewise, the concurrent use of cortisone and phenylbutazone did not appear to alter the toxicity of either substance. In fact, when cortisone and phenylbutazone are used concurently smaller doses of each appear to be effective. When therapy is changed from cortisone or corticotropin to phenylbutazone, the dosage should be slowly reduced and continued during the first week of phenylbutazone administration to avoid exacerbation of symptoms.

SUMMARY AND CONCLUSIONS

Phenylbutazone was administered to 800 patients with a variety of diseases.

Clinical usefulness of phenylbutazone was evaluated by relating therapeutic response to toxicity. On this basis, it was found to be much more useful in gout than in any other disease in which it was studied. It is our opinion that this is the drug of choice in the treatment of this disease. Phenylbutazone also was clinically useful, but to a lesser extent, in psoriasis with arthritis, ankylosing spondylitis, rheumatoid arthritis, and painful shoulder. Its use in malum coxae senilis, osteoarthritis, osteoporosis, and mixed arthritis is limited by a greater incidence of toxicity without a commensurate degree of clinical improvement.

Among the 800 patients 321 (40%) exhibited 457 untoward side-effects. It was necessary to discontinue medication owing to toxicity in 121 patients (15%). The most frequently encountered reactions included water retention, nausea, rash, epigastric pain, vertigo, and stomatitis. Unusual severe reactions included peptic ulcer activation (1%) with bleeding in three patients (0.37%), hepatitis (0.25%), hypertension (1.3%), transient psychosis (0.25%), leucopenia of moderate severity (2.1%), agranulocytosis (0.6%), thrombocytopenia (0.12%), and purpura without thrombocytopenia (0.5%). Toxic side-effects were seen in females more frequently than in males.

All the five patients with agranulocytosis recovered following discontinuance of medication. In three of these patients phenylbutazone therapy was later resumed without untoward effect.

The frequent occurrence of minor untoward side-actions and the infrequent occurrence of severe toxic manifestations necessitate careful supervision of patients receiving phenylbutazone.

GASTROINTESTINAL HEMORRHAGE AS A COMPLICATION OF POLIOMYELITIS

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DURING the summer and fall of 1952 this community was the center of a severe epidemic of poliomyelitis. The Chelan and Douglas County health departments received reports of 172 cases (the 1950 census for Chelan County was 39,301, and for Douglas County 10,817). Records at the Central Washington Deaconess Hospital, which included patients from other counties, revealed 148 bed patients; 29 outpatients not hospitalized; 16 respirator patients, of which there were 7 at one time; 54 suspects (not proved), and 8 patients who died. Of these eight, five patients presented as a terminal complication gastrointestinal hemorrhage. The case reports follow.

CASE 1.—A 6-year-old white boy was admitted on Sept. 4 with a history of listlessness, fever (temperature up to 103 F.), and a headache of three days' duration. Penicillin was given the day prior to admission.

Initial physical examination in the hospital revealed a listless, drowsy child with marked stiffness of the neck and back muscles. The cranial nerves were intact, and the deep and superficial reflexes were equal and active. The temperature was 102.4 F. (rectal). Initial hemoglobin level was 14.5 gm., and the white blood cell count was 18,200, with 77% polymorphonuclear leucocytes, 17% lymphocytes, and 6% stab cells. Except for a trace of albumin the results of urinalysis were normal. Spinal fluid examination revealed 117 cells per cubic millimeter, with 19% polymorphonuclear leucocytes, 81% lymphocytes, and a total protein of 218 mg.

Initial treatment consisted of 10 cc. of convalescent serum intramuscularly, hot packs, and penicillin. Within the first 48 hours the intercostal muscles and muscles of the upper spine and both arms became involved. Nasal suction and oxygen were necessary. On the fifth hospital day the patient was placed in a respirator and intravenous fluids were given to correct dehydration. On the ninth day urinary cystitis developed which was treated with a sulfonamide drug. By the fourteenth hospital day the patient was out of the respirator for 30 minutes and was able to begin physiotherapy. During the next three days the patient was occasionally cyanotic. On the morning of the 17th hospital day the abdomen was distended and the patient was irrational and cyanotic. Gastric suction was begun; "coffee ground" colored material was obtained. The temperature rose to 100 F., and the general condition remained poor. Neostigmine (Prostigmine), vitamin K, antacids, and epinephrine (Adrenalin) were administered. The patient died on the evening of the 17th hospital day.

CASE 2.—A 24-year-old white man was admitted to the hospital on Sept. 6 with complaints of general malaise, headache, backache, sore throat, abdominal pain, and fever of 24 hours' duration. At the onset of symptoms the patient was given penicillin for an inflamed pharynx.

Initial examination revealed a well-developed acutely ill patient with marked nuchal rigidity and a questionable right Kernig's sign. The spinal fluid contained 157 white blood cells per cubic millimeter (differential cell count was not recorded) and total protein of 196 mg. per 100 cc. Upon admission the patient was given immune globulin, and this was repeated again in eight hours.

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On the first hospital day there was extensive paralysis of the abdominal muscles, both psoas groups, the gluteal muscles, the right hamstrings, and the right quadriceps group. The patient was unable to void, and a retention catheter was inserted. Intercostal breathing developed, and in the evening the patient was placed in a respirator. The temperature rose to 103 F. on the second day, and all the extremities showed extensive paralysis; the patient was still able to swallow, talk, and move his head. On the third and fourth hospital days the patient was frequently cyanotic and irrational. Oxygen was given, and frequent suctioning of mucus from the nose and mouth was necessary. A tracheotomy was done on the fifth day; a large mucus plug was aspirated, and the patient's color improved. When the tracheal tube was removed later that evening the color remained good. On the sixth day the patient vomited dark red material and became cyanotic, and the cyanosis persisted in spite of tracheal aspiration. Cyanosis and vomiting persisted, and just prior to death there was a slight amount of subcutaneous emphysema.

CASE 3.—A 30-year-old white man was admitted to the hospital on Sept. 7 with complaints of malaise, weakness, intermittent headache, and stiffness of the neck of 48 hours' duration. One week prior to admission the patient had follicular tonsillitis treated with chlortetracycline (Aureomycin). Initial examination revealed a well-developed apprehensive white man with moderate nuchal rigidity, abdominal distention, and right quadriceps weakness. Except for albumin 2+ the urine was normal. The white and red blood cell counts were normal. The spinal fluid was cloudy and showed 800 white blood cells per cubic millimeter, increased globulin, glucose 49 mg. per 100 cc., and a differential cell count of 51% lymphocytes and 49% polymorphonuclear leucocytes. A Gram stain of spinal fluid sediment revealed no bacteria.

The entire course was febrile, with temperature ranging from 99 to 100.3 F. and terminally to 103.2 F. On the first hospital day the patient had difficulty voiding and a retention catheter was inserted. Suggestive weakness of the right upper extremity was noted on the second day. By the afternoon of the third day the patient became dyspneic and cyanotic and suction was used to clear the throat of mucus. On the fourth day the patient was restless and confused and was placed in a respirator. Early in the morning of the fifth day increased abdominal distention was noted and the patient vomited an estimated 2 qt. (1.9 liters) of bright red bloody-appearing fluid. A stomach tube was inserted and drained dark brown liquid which was strongly acid and positive for occult blood. On the fifth day the patient suddenly became deeply cyanotic and died.

An autopsy was performed. The lung fields showed gross and microscopic evidence of hyperemia and atelectasis. Microscopic sections of the liver showed central hyperemia and degeneration of the inner third of the lobule. The adrenal gland was more friable than normal, and the cortex was narrow. However, there was a reasonable amount of lipid present in the cortical cells. When the stomach was opened the pyloric surface was seen to be covered by soft amorphous black flecks of material which could be easily wiped away. The underlying mucosa was involved with numerous shallow 2 to 5 mm. hemorrhagic ulcerations. The brain and spinal cord were not examined. The remainder of the abdominal organs were not remarkable.

CASE 4.—A 42-year-old white woman was admitted from another hospital on Sept. 17 with history of illness for one week, fever of 48 hours' duration, and loss of consciousness and gastric hemorrhage for the preceding 24 hours.

Initial physical examination was limited because of the patient's poor condition. No reflexes were elicited. The patient was unconscious. The pupils were 2 mm., regular, and fixed. Immediate treatment consisted of placing the patient in a tank-type respirator, giving oxygen by catheter, and performing a tracheotomy. Vitamin K, 72 mg., was given intravenously. On the first hospital day the temperature fell from 103.4 to 99 F., the color seemed improved, and fibrillary muscle twitchings were noted. On the second day the pupillary reflexes returned and the patient opened and closed her eyes on command. Although semicomatose, she moved all of her extremities. On the fourth day there was a temperature of 101 F. and there were signs of pneumonia; penicillin was given. Antacids (sodium carboxymethylcellulose [Carmethose], aluminum hydroxide preparation [Amphojel], milk and cream) were given through the stomach tube. By the sixth day the gastric drainage was greenish-brown mucus. For the next four days the patient continued febrile, was cyanotic, and responded in an irrational manner. There was no more gross blood in the gastric drainage. On the 11th day the patient's pulse became weaker, cyanosis increased, and there was increased mucus in the bronchial tree and the patient died.

CASE 5.—A 33-year-old white man was admitted to the hospital on Nov. 3 because of an illness of one week's duration, beginning with epigastric pain, nausea, and sore throat. Two days prior to admission he had headache and pains in the legs and hips.

Physical examination revealed a febrile patient with acetone breath, rigid neck, and increased generalized muscle tone. The urine showed 2+ albumin; but was otherwise normal. The routine blood cell counts were normal. Spinal fluid examination revealed a definite increase in globulin and 295 white blood cells per cubic millimeter (the differential cell count was not given). Gram stain of the spinal fluid showed no organisms.

On the first hospital day the patient was nauseated, retained little by mouth, and had to be catheterized because of inability to void. On the second day the patient was placed in a respirator. The patient complained of a "stomach ache" on the fourth day; gastric suction was used, and the return consisted of brown liquid with some blood. A tracheotomy was done. From the fourth to the seventh days the patient was occasionally cyanotic and irrational. The gastric tube continued to drain dark brown and occasionally bright red fluid. On the seventh day the patient's pulse and respirations became shallow and irregular and he died.

COMMENT

In a recent epidemic of poliomyelitis, five of eight deaths were complicated by gastrointestinal hemorrhage. In one case the gastric secretions were strongly acid and at autopsy hemorrhagic gastritis was observed. A review of the literature reveals that Dublin and Larson [1] emphasized lesions other than those of the central nervous system in a paper published in 1943. In their 12 cases the lymph follicles were regularly and markedly hypertrophied, but they made no mention of gastric lesions. Saphir,[2] in commenting on postmortem examinations of 17 patients who died of clinically diagnosed poliomyelitis, found marked hyperplasia of the lymph follicles of the intestinal tract, of Peyer's patches, and of the peritoneal lymph nodes. These findings were more common in children. Again, no mention was made of gastrointestinal ulceration.

Heyde and Robinson,[3] in a paper published in 1948, apparently reported the first two cases in the English literature of ulceration of the gastrointestinal tract as a complication of poliomyelitis. One of these patients, an adult man, had multiple duodenal ulcers, and the other patient, a 4½-year-old girl, had a perforation of the stomach at the esophageal junction. Erskine, Mason, and McDade [4] in 1950 reported two cases of bulbar poliomyelitis in young adults who at autopsy were found to have esophageal ulcers. They concluded that regurgitation of hydrochloric acid and pepsin, with autolytic digestion, was a most likely possibility as to etiology of the ulceration. Contributing factors were recumbent and Trendelenburg position; phrenic nerve paralysis, which allowed relaxation of the cardia and thus facilitated regurgitation of the stomach contents; fear (to a very minimal extent because of the acuteness of the disease); trauma due to suction tubes, and mechanical action of the respirator, a factor which may produce actual perforation although it does not initiate ulcer formation. They tend to disregard direct action of the virus since "there is no evidence of polio virus producing ulcerative effect in the gastrointestinal tract." This

1. Dublin, W. B., and Larson, C. B.: Pathologic Findings in Poliomyelitis, Am. J. Clin. Path. **13**:15, 1943.

2. Saphir, O.: Visceral Lesions in Poliomyelitis, Am. J. Path. **21**:99, 1945.

3. Heyde, E. C., and Robinson, S.: Acute Peptic Ulceration Accompanying Bulbar Poliomyelitis: Report of 2 Cases, Gastroenterology, **11**:519, 1948.

4. Erskine, F. A.; Mason, J. H., Jr., and McDade, H.: Perforation of Esophageal Ulcers in Bulbar Poliomyelitis: Report of 2 Fatal Cases, Am. J. Med. **8**:239, 1950.

is in contradistinction to the view of Bower,[5] who states that gastritis occurs quite regularly in patients dying of poliomyelitis. Bower believes the etiology to be virus in origin since "tests on many hundreds of these patients show that almost invariably hydrochloric acid is lacking."

Cook and co-workers [6] report on five cases of gastrointestinal hemorrhage complicating poliomyelitis, with survival of one patient. The four deaths were from a review of 54 cases of acute poliomyelitis with postmortem examinations at the (Boston) Children's Hospital from 1916-1950. Of these four, three had esophageal ulcers and the fourth showed petechial hemorrhage in the ileum.

In discussing the etiology Cook and co-workers state that gastrointestinal perforation in poliomyelitis has always been associated with respiratory center involvement and has not been seen with less severe bulbar poliomyelitis. They believe gastric intubation did not play a role in the development of this lesion. Likewise, they do not believe the respirator or other external trauma played a role, since some convalescent patients spend months or years in respirators without the lesion developing. Anoxia alone also seems unlikely, since "in the experience of Children's Hospital severe cyanosis in itself has not led to esophageal or gastric perforation." Finally, they state that reflex of gastric contents into the esophagus seems unlikely, because of lack of pathologic confirmation. Although gastric contents can give rise to esophagitis and ulceration, chronicity is an important factor, and chronicity has not been present in these patients. Their conclusion is that midbrain damage is related to gastrointestinal lesions, as emphasized by Cushing.

When gastrointestinal bleeding occurs as a complication of poliomyelitis it is a severe omen. Of the seven patients previously reported only Cook's patient survived. None of our five patients survived, although in one hemorrhage did stop. Rational treatment will be improved when the etiology is better understood. Erskine and co-workers,[4] believing that autolytic digestion is the important factor, recommended the following treatment: (1) antacides and modified Sippy regimen for all patients in respirators; (2) semi-Fowler position when possible; (3) tracheotomy with oxygen by catheter early and placement in the respirator only as a last resort; (4) chemotherapy, since in case of perforation medical rather than surgical management is imperative. Cook and co-workers,[6] emphasizing midbrain damage, treated their patient with blood transfusions, ulcer regimen, vitamin K, and atropine. In the present series Patient 4 was given vitamin K and antacids, was placed in a respirator, and had a tracheotomy. It is to be emphasized that the bleeding stopped while the patient was in the respirator.

SUMMARY

Five cases of acute bulbar poliomyelitis associated with gastrointestinal hemorrhage are presented. The exact cause of this phenomenon is not known, but several possibilities are presented.

Drs. Edward W. Nash, J. T. Abraham, Robert E. Bolton, and L. C. Miller gave permission to report their cases.

5. Bower, A. G.: Personal communication to the author.

6. Cook, C. D.; Hartman, J. R.; Sarnoff, S. J., and Berenberg, W.: Gastrointestinal Lesions in Acute Bulbar Poliomyelitis: Report of Five Cases with Recovery in One, Pediatrics **7**:415, 1951.

GLUCAGON, THE HYPERGLYCEMIC AGENT IN PANCREATIC EXTRACTS

A Possible Factor in Certain Types of Diabetes

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AND
J. Z. RUTMAN, B.S.
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WITHIN the past 30 years tremendous strides have been made in our understanding of the pathways of intermediary metabolism and, more recently, in the study of the metabolic disturbances which may occur in disease. Despite the many studies which have been performed since the isolation of insulin, an understanding of the biochemical disturbances which occur in the diabetic patient is not forthcoming. The earlier concept, that this syndrome is produced by a simple insulin deficiency, has given way to the belief [1] that in some instances various other factors may play a role. Among these may be glucagon, the hyperglycemic-glycogenolytic factor.

Soon after Banting and Best [2] extracted insulin from the pancreas, it became apparent that the crude preparations available contained an impurity which caused a rise in blood sugar level. Bürger and his co-workers [3] and Collens, Murlin, and their associates [4] studied this "contaminant," which they called glucagon. After Abel [5] succeeded in preparing a crystalline insulin preparation which was free of this activity, it was assumed that American insulins contained none of this material, which was considered by many to be a nonspecific agent present in tissue extracts and which was largely neglected in this country. In 1946 de Duve and his asso-

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1. (*a*) Bornstein, J., and Lawrence, R. D.: Plasma Insulin in Human Diabetes Mellitus, Brit. M. J. **2**:1541 (Dec. 29) 1951. (*b*) Wrenshall, G. A.; Bogoch, A., and Ritchie, R. C.: Extractable Insulin of Pancreas, Diabetes **1**:87 (March-April) 1952.

2. Banting, F. G., and Best, C. M.: The Internal Secretion of the Pancreas, J. Lab. & Clin. Med. **7**:251 (Feb.) 1922.

3. Bürger, M., and Kramer, H.: Über die Wirkungsverschiedenheit technischer Insuline und kristallisierter Präparate bezüglich der primären Insulinhyperglykämie, Arch. exper. Path. u. Pharmakol. **156**:1, 1930.

4. Collens, W. S., and Murlin, J. R.: Hyperglycemia Following the Portal Injection of Insulin, Proc. Soc. Exper. Biol. & Med. **26**:485 (March) 1929.

5. Abel, J. J.; Geiling, E. M. K.; Roviller, C. A.; Bell, F. F., and Wintersteiner, O.: Crystalline Insulin, J. Pharmacol. & Exper. Therap. **31**:65 (May) 1927.

ciates [6] noted that insulin prepared in the NOVO laboratories in Denmark differed in some of its actions from American insulins which they tested, and they found that these differences could be accounted for by small amounts of an impurity present in the American insulins. Since that time many studies have been performed confirming many of the older observations and amplifying the former studies. It has been suggested by a number of observers that this material is derived from the alpha cells of the islets of Langerhans. Since much of this work has been reviewed elsewhere,[7] only the pertinent and more recent observations will be discussed here.

CLINICAL OBSERVATIONS

It has been observed repeatedly [8] that patients who survive total pancreatectomy require relatively small amounts of insulin (25 to 40 units) for control of their diabetic state. Indeed, several patients who had previously been diabetic were found to have a somewhat lower insulin requirement after pancreatectomy. In some instances it seems likely that the alteration of the nutritional status associated with an absorptive defect caused by pancreatic insufficiency may be the cause of the lowered insulin requirement; in others rather good control of this disturbance appears to have been attained with no increase in insulin need. The human deprived of his pancreas is quite sensitive to insulin; consequently a small overdose may produce insulin shock; withholding insulin, however, results in the early appearance of diabetic acidosis.

These observations suggest that a pancreatic factor, in addition to insulin, may play a role in the diabetic state. By analogy, it might be that the patient with clinical diabetes of unknown etiology, the young thin diabetic with a tendency to go into coma or shock readily, resembles the pancreatectomized person, whereas the disturbance in the stable diabetic who may require very large doses of insulin, who is older and frequently obese and in whom coma may fail to develop for a prolonged period of time after insulin is withdrawn, resembles the chemically induced diabetes of animals, in which only the insulin mechanism has been disturbed. That these two factors alone do not account for all findings in patients with diabetes is evident, but it seems quite possible that a relative insufficiency of one of these pancreatic factors may in part account for some unexplained observations in clinical diabetes.

Glucagon was administered to a group of normal persons, to patients with stable diabetes and with labile diabetes, and to a small group of patients with miscellaneous conditions.[9] We found that the normal group and the patients with stable diabetes had a similar, moderate rise in blood sugar level, whereas patients with labile

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7. (*a*) Pincus, I. J.: A Hyperglycemic Factor Extracted from the Pancreas, J. Clin. Endocrinol. **10**:556 (May) 1950. (*b*) Sutherland, E. W.: Action of HG Factor and Epinephrine, in Recent Progress in Hormone Research, edited by G. Pincus, New York, Academic Press, Inc., 1950. (*c*) Weisberg, H. F.; Caren, R.; Huddleston, B., and Levine, R.: Effects of Hyperglycemic-Glycogenolytic Factor (HGF) Found in Insulin Preparations, Am. J. Physiol. **159**:98 (Oct.) 1949. (*d*) Zimmermann, B.: Endocrine Functions of the Pancreas, Springfield, Ill., Charles C Thomas, Publisher, 1952.

8. Gaston, E. A.: Total Pancreatectomy, New England J. Med. **238**:345 (March 11) 1948.

9. Pincus, I. J.: Effect of Hyperglycemic-Glycogenolytic Factor on Blood Sugar of Patients with Diabetes, Proc. Soc. Exper. Biol. & Med. **74**:377 (June) 1950.

diabetes had a more marked rise in blood sugar level. Kirtley, Waife, Helmer, and Peck,[10] in a more elaborate study employing highly purified glucagon, found a decreased response in the patients with labile diabetes. They tested their patients in the fasting state, whereas ours had been given their usual breakfast and insulin. These studies should be repeated on the same patients, but they suggest that the patient with labile diabetes may have a marked variability in hepatic glycogen stores or in that portion of the glycogen which can be mobilized readily by this mechanism. This may account, at least in part, for some variations noted in clinical diabetes.

EXPERIMENTAL DIABETES

A number of observations which have been made in experimental diabetes also suggest that pancreatic factors other than insulin may play a role in the diabetic state. Young [11] observed the extremely high insulin requirement of dogs made diabetic by the repeated injection of anterior pituitary extracts. He also called attention to the fact that when insulin is withheld from such an animal relatively little ketosis develops. Following removal of the pancreas from such a diabetic animal the insulin requirement decreased; the hyperglycemia which occurred when insulin was withheld was less marked, but acidosis readily developed. Similar observations were made by Dragstadt and co-workers [12] on the insulin requirement of dogs subjected to extensive (but not total) pancreatectomy as compared with that of animals subjected to total pancreatectomy. Thorogood and Zimmermann [13] performed similar experiments on dogs made diabetic by the injection of alloxan, a chemical agent which destroys the beta, or insulin-producing, cells and causes a severe "diabetes" in the dog. Their observations were similar to those of Young, in that the insulin requirement was frequently much higher than in pancreatectomized animals. Furthermore, when insulin was withheld from such animals relatively little acidosis resulted, whereas when the pancreas was removed from the alloxan-diabetic dog the insulin requirement decreased, the blood sugar level was more labile, and, if insulin was now withheld, a severe acidosis developed. These authors also performed a critical experiment on one animal, which has been confirmed and amplified by the work of Candela and his collaborators.[14] They tied the pancreatic ducts of an alloxan-diabetic dog and found no significant difference in the insulin requirement nor in the rapidity of development of acidosis. This eliminated the external secretion of the pancreas as the agent responsible for the decreased tendency to acidosis. When the fibrotic pancreas was removed the

10. Kirtley, W. R.; Waife, S. O.; Helmer, O. M., and Peck, F. B.: Effect of Purified Hyperglycemic-Glycogenolytic Factor (Glukagon, HGF) on Carbohydrate and Corticoid Metabolism in Normal and Diabetic Subjects, presented before the American Diabetes Association, New York, May 31, 1953.

11. Young, F. G.: The Anterior Pituitary Gland and Diabetes Mellitus, New England J. Med. **221**:635 (Oct. 26) 1939.

12. Dragstedt, L. R.; Allen, J. G., and Smith, E. M.: Extensive Insulin Tolerance in Diabetic Dogs, Proc. Soc. Exper. Biol. & Med. **54**:292 (Dec.) 1943.

13. Thorogood, E., and Zimmermann, B.: The Effects of Pancreatectomy on Glyclosuria and Ketosis in Dogs Made Diabetic by Alloxan, Endocrinology **37**:191 (Sept.) 1945.

14. Candela, J. L. R.; Goni, P. M.; Caldeiro, M. R., and Gonzalez Carreras, P.: Requerimiento de insulina antes y después de la pancreatomia total, y previa ligadura de los conductos pancreáticos, en perros diabéticos por aloxana, Trab. Inst. Nac. cienc. Med., 1947, Vol. 9.

animal became more sensitive to insulin, and when insulin was withheld acidosis developed rapidly. We have in part confirmed these findings and are of the impression that there is a marked difference between alloxan-diabetic animals and pancreatectomized animals. It seems that the lack of development of acidosis in the alloxan-diabetic animal is the result of some factor in addition to insulin.

Mirsky and co-workers [15] suggested that the relative lack of development of ketosis in the alloxan-diabetic animal is due to differences in absorption of protein and of other carbohydrate precursors and possibly results from changes in hepatic glycogen stores. This explanation does not account for the differences between the alloxan-diabetic animal with the pancreatic ducts ligated and the pancreatectomized animal. Furthermore, we have observed, as have others,[16] an actual increase in the liver glycogen levels above the normal in some of the alloxan-diabetic rabbits which we have studied. These findings suggest that a more complex disturbance is produced in these animals than can be accounted for by removal of insulin alone.

PANCREATIC EXTRACTS

Insulin is an extract of the pancreas. We have tested many lots of commercial American insulin and have been able to demonstrate glucagon in every sample studied. We have also tested a number of lots of the Danish NOVO insulin and found variable but relatively small amounts of this material. One lot of specially prepared insulin made by Eli Lilly & Company is apparently free from this material. Olsen and Klein [17] found that when insulin is injected intravenously there is a transient hyperglycemia. The hypoglycemic action of commercial insulin can be destroyed by incubation at an alkaline pH or by the addition of cysteine.[18] We [7a] have confirmed these findings but have found that careful study of the preparations obtained in this manner generally reveals small amounts of residual insulin activity. Figure 1 compares the effect of the intravenous injection of a commercial insulin containing a relatively large amount of glucagon with the injection of a similar amount of the same preparation after inactivation by heat and alkali. It would appear that when the pancreas is extracted to produce insulin the extract contains variable amounts of glucagon as a contaminant of the insulin.

Extracts were prepared from normal dog pancreas. Similar preparations were made from the pancreas of the fetal calf and from dog pancreas rendered fibrotic by ligating the pancreatic ducts. Pancreas obtained from dogs previously treated with alloxan were extracted in a similar fashion. Comparable preparations were also made from the parotid glands of dog and steer as well as from liver, kidney, and muscle. Figure 2 shows the characteristic effect of these extracts on the blood

15. Mirsky, I. A.; Futterman, P.; Wachman, J., and Perisutti, G.: The Influence of Pancreatectomy on the Metabolic State of the Alloxan Diabetic Dog, Endocrinology **49**:73 (July) 1951.

16. Morita, Y., and Orten, S. M.: Glycogen Content of Liver of Alloxan Diabetic Rat, Am. J. Physiol. **161**:545 (June) 1950.

17. Olsen, N. S., and Klein, J. R.: Hyperglycemia Induced by Certain Insulin Preparations, Proc. Soc. Exper. Biol. & Med. **66**:86, 1947.

18. Bürger, M., and Brandt, W.: Über das Glukagon (die hyperglykämisierenden Substanz des Pankreas), Ztschr. ges. exper. Med. **96**:375, 1935. Sutherland, E. W., and Cori, C. F.: Influence of Insulin Preparations on Glycogenolysis in Liver Slices, J. Biol. Chem. **172**:737 (Feb.) 1948.

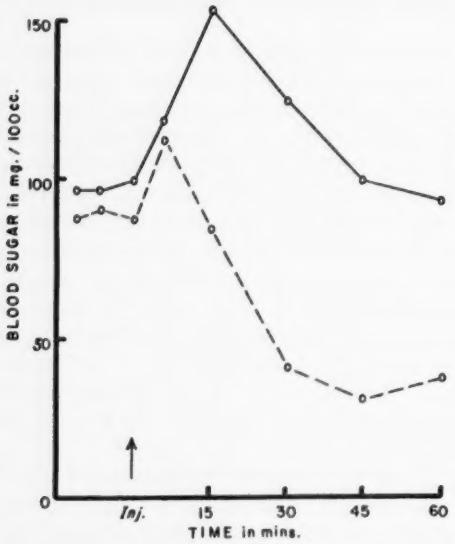

Fig. 1.—Change in blood sugar level following the intravenous administration of 10 units of commercial insulin (broken line) compared with the injection of an equivalent amount of the same preparation after it had been heated at an alkaline pH (solid line).

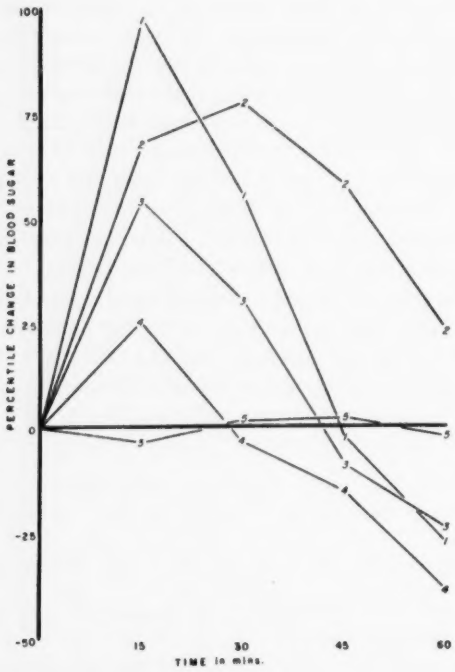

Fig. 2.—Percentile change in blood sugar level after the intravenous injection of extracts prepared from 6.5 to 7 gm. of (1) fetal calf pancreas, (2) pancreas obtained from an alloxan-diabetic dog, (3) fibrotic pancreas obtained from a dog three months after ligation of the pancreatic ducts, (4) pancreas from a normal dog, and (5) normal dog parotid gland.

sugar level of a dog. It will be noted that the preparations from normal, fetal calf, and fibrotic pancreas all contain insulin as well as glucagon. Extracts prepared from the alloxan-diabetic pancreas contain extremely small amounts of insulin, and its effect is entirely masked by the marked hyperglycemia which results. Sutherland and co-workers [19] have found glucagon in the gastric and duodenal mucosa, where cells resembling alpha cells have been found. These experiments lead us to believe that the hyperglycemic factor may be extracted from normal pancreas and from the pancreas after the acinar tissue has been largely destroyed by duct ligation or before it is functional in the fetal calf and that it is present after the insulin-producing beta cells have been destroyed but that it is not present in other tissues, with the possible exception of gastric and duodenal mucosa.

MECHANISM OF ACTION

Several groups of investigators [20] have been concerned with the mechanism of action of glucagon. It has been noted that the intravenous injection of the substance causes a rise in the blood sugar level of a normal dog (Fig. 3). It will be noted, however, that when comparable amounts of this substance are administered to an animal after a 96-hour fast, when the hepatic glycogen levels might be expected to be quite low, there is little change in the blood sugar level. This material also produces a prompt elevation of the blood sugar when injected intravenously into a pancreatectomized animal well-maintained with insulin and "primed" by the administration of additional glucose. When it is given to the same animal after it has been permitted to go into acidosis, by withholding insulin, there is relatively little response. Following hepatectomy glucagon produces no significant rise of blood sugar level. It has also been demonstrated (Fig. 4) that this substance can, at least in part, prevent the fall in blood sugar level following the administration of small doses of insulin. The preparation must, however, be given by continuous infusion or by repeated injection, and the animal must have been well fed and healthy. The route of administration is also of importance. We have found that, when employed in a dose capable of producing a brief but maximal elevation of blood sugar level, the portal injection produces a more prolonged elevation than the intravenous injection, whereas the intraperitoneal injection results in a less marked and a delayed elevation of blood sugar level. The intramuscular injection is much less effective, and subcutaneously the material is minimally effective.

Sutherland and Cori [21] have studied the mechanisms whereby glycogenolysis is effected. The addition of glucagon to the medium bathing the liver slice results in a more rapid breakdown of glycogen and liberation of glucose than occurs in a control preparation. These workers also studied the enzyme systems involved and found that glucagon increases the activity of hepatic phosphorylase, either by preventing the inactivation of this enzyme or by reactivating an inactive phosphorylase.

19. (*a*) Sutherland, E. W., and de Duve, C.: Origin and Distribution of the Hyperglycemic-Glycogenolytic Factor of the Pancreas, J. Biol. Chem. **175**:663 (Sept.) 1948. (*b*) Sutherland, E. W.; Cori, C. F.; Haynes, R., and Olsen, N. S.: Purification of the Hyperglycemic-Glycogenolytic Factor from Insulin and Gastric Mucosa, ibid. **180**:825 (Sept.) 1949.

20. (*a*) Zimmermann, B., and Donovan, T. J.: Hyperglycemic Effect of Insulin, Am. J. Physiol. **153**:197 (May) 1948. (*b*) Footnote 7*a* and *c*. (*c*) Ferner, H.: Studien über die Histophysiologie des Inselsystems der Bauchspeicheldrüse und den Diabetes mellitus, Virchows Arch, path. Anat. **319**:390, 1950.

21. Sutherland, E. W., and Cori, C. F.: Effect of Hyperglycemic Glycogenalytic Factor and Epinephrine on Liver Phosphorylase, J. Biol. Chem. **188**:531 (Feb.) 1951.

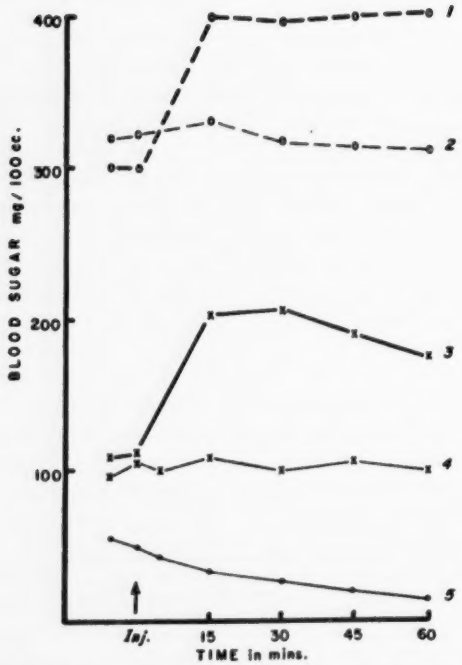

Fig. 3.—Effect of injecting glucagon on the blood sugar level of (1) a pancreatectomized dog well-maintained with insulin and glucose, (2) the same dog after insulin was withdrawn, (3) a normal dog, (4) the same dog after a 96-hour fast, and (5) a dog after evisceration and hepatectomy.

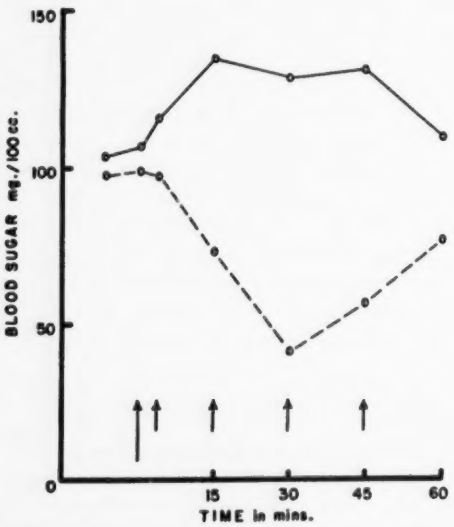

Fig. 4.—Change in blood sugar level of a 10 kg. dog after the intravenous injection of 1 unit of insulin (broken line) and after the injection of 1 unit of insulin followed by the repeated injection of glucagon (solid line).

It appears as though glucagon and epinephrine act on the same mechanism in this system. It seems to us to be worthy of note that phosphorylase may bring about the formation of glycogen from glucose-1-phosphate and that the net effect of this reaction presumably depends upon a number of factors, including the amounts of sugar or other precursors available.

Considerable evidence has been discussed which suggests that glucagon may affect acidosis. Zimmermann and Donovan [20a] found that this material produces a rise in the level of acetone bodies in the blood, which they attribute to a decrease in the available liver glycogen. Foa and Weinstein [22] also failed to demonstrate any ameliorating effect of glucagon on acidosis. Rutman [23] reported on studies from our group with similar results. There appear to be no reports demonstrating a decreased acidosis due to the administration of this material to acidotic animals. We also attempted to prevent the occurrence of acidosis by repeated administration of large amounts of this material, to no avail.

It seems to us that a study of the effect of glucagon on lipid metabolism should be informative. Haugaard and Stadie [24] noted that glucagon decreases the hepatic synthesis of fatty acid from labeled acetate. They suggested that this may result from the loss of hepatic glycogen rather than from a direct effect on the synthetic mechanism. We studied the effect on blood and liver lipids of administering glucagon preparations to normal and pancreatectomized dogs. The preparations, which contained small amounts of insulin, produced a decreased acidosis and a return of blood and liver lipids towards normal. It became apparent, however, when equivalent amounts of insulin were administered, that a similar effect was produced in the lipid values with little effect on blood sugar values.

These observations imply that the amount of insulin necessary for the regulation of lipid metabolism and ketone body formation is less than that required for the maintenance of a normal blood sugar level. As suggested by Mirsky and co-workers,[15] this may explain why, in chemically-induced diabetes in the dog and in stable human diabetes in which there is demonstrable circulating insulin in the blood [1a] and ample stores of insulin in the pancreas,[1b] acidosis does not develop readily. The very high sugar levels in such instances may be produced, however, by the second pancreatic hormone. We have concluded that either glucagon has no effect on lipid metabolism or that the effect produced is an indirect one and too subtle to be apparent when studied by the methods at our disposal.

Several pertinent additional observations have been made on the mode of action of this material. We have studied the blood pressure response and have found no change after the administration of large doses of this material; nor have we found any effect on the eosinophile count in the human. Kirtley and his associates [10] also studied the effect of this substance on blood lactate and pyruvate in comparison with the effect of epinephrine. They found no rise in either of these constituents after administration of glucagon, hence this material has no epinephrine-like action on muscle glycogen.

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22. Foa, P. P., and Weinstein, H. R.: Metabolic Effects of an Insulin Free Pancreatic Extract, Am. J. Physiol. **163**:711 (Dec.) 1950.

23. Rutman, J. Z.; Pincus, I. J.; Brown, L., and Scott, M.: Effect of HGF on Acidosis and Lipids in Intact and Depancreatized Dogs, Federation Proc. **12**:121 (March) 1953.

24. Haugaard, E. S., and Stadie, W. C.: The Effect of Hyperglycemic-Glycogenolytic Factor and Epinephrine on Fatty Acid Synthesis, J. Biol. Chem. **200**:753 (Feb.) 1953.

IS GLUCAGON PHYSIOLOGICALLY ACTIVE?

The fact that a substance can be extracted from tissue and has certain effects on enzyme systems does not conclusively prove that the substance in question is hormonal in nature. There is some evidence, however, that glucagon is a hormone. Foa [25] and his collaborators performed cross-circulation experiments using alloxan-diabetic dogs as donors. Their findings suggest that pancreatic vein blood can elevate the blood sugar level of a normal animal. These observations are very suggestive but not entirely conclusive. Bornstein [26] found that pancreatic vein blood obtained from cats treated with growth hormone had high concentrations of a substance which elevated the blood sugar of the sensitive test animals which he employed for assaying blood insulin levels. In a further group of observations from Foa's laboratory [27] cross-circulation experiments showed more conclusively that the pancreatic vein blood contains a blood-sugar-elevating substance, particularly when insulin is given the donor dog, and, conversely, that glucagon injected into the donor dog produces a drop in the blood sugar level of the recipient. These findings not only seem quite conclusive but suggest that the secretions of glucagon and insulin maintain a relationship to each other and also may be controlled by other factors, such as growth hormone.

CELLULAR ORIGIN OF GLUCAGON

The alpha cell of the islets of Langerhans is a cell which contains secretory granules and would appear to be functioning actively and which has been suggested [28] to be the source of this factor. The direct evidence that the alpha cell is the cell of origin of this material, however, is not entirely convincing. Lieber [29] studied the pancreas of a number of alloxan-diabetic rabbits which we had observed over a prolonged period of time. After several months some of the very diabetic animals showed marked degranulation and swelling of the alpha cells. No change in their clinical state had been observed, and the blood sugar levels had not been depressed. Kadota and Midorikawa [30] observed that the injection of diethyldithiocarbamate produces a selective destruction of the alpha cells, with at first a rise in blood sugar level, presumably occurring when the cells are destroyed and preformed glucagon is liberated, followed by a fall in blood sugar level, presumably produced by the unopposed action of insulin thereafter. We attempted to repeat these observations by injecting the substance intravenously into rabbits previously made diabetic by alloxan. Those animals which survived were in very poor clinical condition and failed to eat, and the drop in blood sugar could, we thought, be attributed to this.

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25. Foa, P. P.; Weinstein, H. R., and Smith, J. A.: Secretion of Insulin and of a Hyperglycemic Substance Studied by Means of Pancreatic-Femoral Cross-Circulation and Experiments, Am. J Physiol **157**:197 (May) 1949.

26. Bornstein, J. E.; Reid, E., and Young, F. G.: The Hyperglycemic Action of Blood from Animals Treated with Growth Hormone, Nature, London **168**:903 (Nov.) 1951.

27. Foa, P. P.; Santa Maria, L.; Weinstein, H. R.; Bergers, E., and Smith, J. A.: Secretion of Hyperglycemic-Glycogenalytic Factor in Normal Dogs, Am. J. Physiol. **171**:32 (Oct.) 1952.

28. Heard, R. D. H.; Lozinski, E.; Stewart, L., and Stewart, R. D.: An Alpha Cell Hormone of the Islets of Langerhans, J. Biol. Chem. **172**:857 (Feb.) 1948. Sutherland and de Duve.[19a]

29. Lieber, M. M.: Lieber, M. M.: Unpublished data.

30. Kadota, I., and Midorikawa, O.: Diabetogenic Action of Organic Reagents: Destructive Lesions of the Islets of Langerhans Caused by Sodium Diethyldithiocarbamate and Potassium Ethylxanthate, J. Lab. & Clin. Med. **38**:671 (Nov.) 1951.

Neither in the animals dying within 24 hours nor in those living for several days and then killed was Lieber [29] able to demonstrate any abnormality in the alpha cells. Van Campenhout and Cornelis [31] have found that cobalt chloride can produce a destruction of the alpha cells, with immediate hyperglycemia and subsequent hypoglycemia. These observations have been confirmed, although the destruction of the alpha cells may not occur in all species. Goldner and co-workers,[32] however, have found that the hyperglycemia produced by cobalt may be reproduced by repeated injection of this material even after the alpha cells have presumably been destroyed by this drug; furthermore, they [33] have found that similar hyperglycemia may be produced in the animal after pancreatectomy and removal of the stomach and duodenum.

These observers [34] have recently extracted the pancreas of animals which had been treated with cobalt, with destruction of the alpha cells, and have found normal amounts of glucagon in these organs. These observations cast doubt upon the alpha cell as the cell of origin of this factor. Much further study remains, therefore, to be done.

CHEMICAL ISOLATION AND STUDY OF GLUCAGON

Because of the difficulty which has been encountered in separating glucagon from insulin by either chemical or physical methods it had been supposed that the two pancreatic hormones were similar proteins, made by cells of similar origin, with, possibly, minor differences in the prosthetic group. In a painstaking and thorough study Staub and co-workers [35] have been able to separate the hyperglycemic factor from insulin by selective precipitation. The highly purified material which they obtained in crystalline form reacts positively to tests for proteins. When administered to a cat in doses of 0.1 γ per kilogram it produces a significant rise in blood sugar, attesting to the remarkable activity of this preparation. The group at the Lilly laboratories are at present engaged in a further study of the material which they have prepared.

PRESENT CONCEPT OF THE POSSIBLE ROLE OF GLUCAGON IN METABOLISM

A review of the literature of islet cell tumors [36] and of carcinoid tumors,[37] which have certain histologic characteristics similar to the alpha cell of the pancreas, reveals a relatively low incidence of diabetes in patients harboring such growths.

31. Van Campenhout, E., and Cornelis, G.: Destruction expérimentale des cellules alpha des ilots endocrines du pancréas chez le cobaye, Compt. rend. Soc. Biol. **145**:933, 1951.

32. Goldner, M. G.; Volk, B. W., and Lazarus, S. S.: The Effect of Cobaltous Chloride on The Blood Sugar and Alpha Cells in the Pancreatic Islets of the Rabbit, Metabolism **1**:544 (Nov.) 1952.

33. Volk, V. W.; Lazarus, S. S., and Goldner, M. G.: Alpha Cell Damage and Blood Sugar Changes in Rabbits After Administration of Cobalt, Proc. Soc. Biol. & Med. **82**:406 (March) 1953.

34. Goldner, M. G.; Volk, B. W., and Lazarus, S. S.: Personal communication to the authors.

35. Staub, A.; Sinn, L., and Behrens, O. K.: Purification and Crystallization of Hyperglycemic Glycogenolytic Factor (HGF), Science **117**:628 (June 5) 1953.

36. Howard, J. M.; Moss, N. H., and Rhoads, J. E.: Collective Review: Hyperinsulinism and Islet Cell Tumors of Pancreas with 398 Recorded Tumors, Internat. Abstr. Surg. **90**:417, 1950, in Surg. Gynec. & Obst., May 1950.

37. Weisberg, H. F., and Schaefer, G. L.: Possible Relationship Between Carcinoid (Argentaffin) Tumors and the Hyperglycemic-Glycogenolytic Factor (HGF), Am. J. Clin. Path. **22**:1169 (Dec.) 1952.

Several patients who had diabetes were found to have islet cell tumors. Adequate staining procedures and extraction of the tumors were not, however, done in these cases.

The possibility that an alpha cell hormone or glucagon may play a role in other clinical conditions has been suggested. Dana and co-workers [38] suggest that it may play a role in the etiology of diabetic retinitis and renal vascular lesions. McQuarrie and his associates [39] have noted an absence or decrease in the number of alpha cells in certain infants with a familial hypoglycemosis. And we have suggested the possibility, as yet not proved, that the hypoglycemia observed in the newborn infant may be due to a similar disturbance, since it has been found that alpha cells are absent from the pancreas in some species at birth and make their appearance only after several days.

A number of observers have suggested that von Gierke's syndrome, which Cori and Cori [40] have shown may be produced by one of several enzymatic defects, may in some instances be caused by a deficiency of the glucagon. Of four patients tested by us or by our associates three have shown no particular response to the administration of this substance. One infant was studied by Paschkis and showed a prolonged and marked rise in blood sugar level after being given a relatively small dose of glucagon. This child has not been available for further study, however, and these observations must certainly be amplified and repeated.

It is probably too early in our studies to state definitely what part glucagon plays in normal metabolism. It would appear to us that under normal conditions, with insulin present, it is an adjunct to insulin rather than an antagonist. Studies at present under way in our laboratory suggest that in the normal animal glucagon causes an increased deposition of glycogen in muscle. In raising the blood sugar level this factor, in effect, makes the hepatic glycogen stores available for insulin activity in the periphery. On the other hand, if insulin is absent or present in relatively small concentrations this substance appears to produce very different effects. It may cause increased liver glycogen formation by activating the phosphorylase, which in an environment of higher blood sugar concentrations may favor the deposition of hepatic glycogen. It seems possible that the marked variability of the glycogen stores [41] in some diabetic patients may account for the acidosis which develops in some patients. Hence, the relative amounts of glucagon and insulin may produce effects similar to those which have been noted in patients with diabetes, and an imbalance of these two substances may explain many of the observations which have heretofore been so difficult to understand.

There is no conclusive evidence that glucagon is a "cause" of diabetes. Pheochromocytomata, however, are commonly associated with diabetes. Since epine-

38. Dana, G. W.; Eversole, S. L., and Zubrod, C. G.: Hyperglycemia and Its Relationship to Diabetic Retinitis and Glomerular Nodules, Bull. Johns Hopkins Hospital **90**:98 (Jan.) 1952.

39. McQuarrie, I.; Bell, E. T.; Zimmermann, B., and Wright, W. S.: Deficiency of Alpha Cells of Pancreas as Possible Etiological Factor in Familial Hypoglycemosis, Federation Proc. **9**:337, 1950.

40. Cori, G. T., and Cori, C. F.: Glucose-6-Phosphatase of the Liver in Glycogen Storage Disease, J. Biol. Chem. **199**:661 (Dec.) 1952.

41. Vallance-Owen, J.: Liver Glycogen in Diabetes Mellitus, J. Clin. Path. **5**:42 (Feb.) 1952.

phrine and glucagon have been shown to influence phosphorylase activity in the same way, this latter substance may play a similar role in occasional cases of diabetes.

It is our impression that this factor is more important as a modifying agent in patients with diabetes than as a causative agent of diabetes.

SUMMARY

Evidence has been presented that a substance, glucagon, which raises blood sugar level, can be extracted from the pancreas and, furthermore, is probably secreted by the pancreas into the pancreatic vein blood. This substance raises blood sugar level by releasing glucose from hepatic glycogen and apparently acts as an adjunct rather than as an antagonist to insulin. It is suggested that the presence of this factor may modify the response of a patient to insulin and possibly to other regulating hormones and may account for some hitherto unexplained phenomena in the diabetic patient. Further study of the physiologic role of this factor is required.

Miss Marjorie Scott, Mrs. Lois Eichengreen, and Miss J. Hurwitz gave technical assistance.

INCIDENCE OF HEPATITIS FOLLOWING USE OF POOLED PLASMA

A Follow-Up Study in Five Hundred Eighty-Seven Korean Casualties

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THE HAZARD of hepatitis in the course of convalescence of a war casualty or otherwise injured person has been generally recognized. This is due mainly to the inadvertent introduction of the virus of hepatitis through the use of nonsterile or poorly cleansed syringes,[1] needles, or surgical instruments and to the injection of blood or blood products such as plasma and thrombin[2] which may contain the virus of hepatitis. This type of hepatitis is distinct from that ordinarily seen and known as epidemic hepatitis. While the hospitalized patient may be exposed to both forms, that which is transmitted by blood or its products seems to be of greater importance and incidence. No accurate studies have been reported, but it is believed that with modern methods of therapy the risk of hepatitis in a hospitalized patient is considerably greater than in a nonhospitalized person under otherwise comparable conditions.

It is well known that the incidence of hepatitis following the use of pooled untreated plasma is high. The risk is increased in direct proportion to the number of donors used in a pool.[3] During the years of World War II and in the period following it was reported that hepatitis developed in 2.5 to 7.3% of recipients of pooled plasma.[4] The risk of hepatitis following the use of blood alone, on

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1. Capps, R. B.; Sborov, V. M., and Scheifley, C. H.: Syringe-Transmitted Epidemic of Infectious Hepatitis with Observations Regarding Incidence and Nature of Infectious Donors, J. A. M. A. **136**:819-824, 1948. Syringe Transmitted Hepatitis, Editorial, ibid. **129**:278, 1945. Morton, R. S.: Syringe Transmitted Jaundice: Inquiry and Plea, Brit. M. J. **2**:938-939, 1948.

2. Lesses, M. F., and Hamolsky, M. N.: Epidemic of Homologous Serum Hepatitis Apparently Caused by Human Thrombin, J. A. M. A. **147**:727-730, 1951.

3. McGraw, J. J.; Strumia, M. M., and Burns, E. B.: The Incidence of Post-Transfusion Serum Hepatitis, Am. J. Clin. Path. **19**:1004-1051, 1949.

4. (*a*) Spurling, N.; Shone, J., and Vaughan, J.: Incidence, Incubation Period and Symptomatology of Homologous Serum Jaundice, Brit. M. J. **2**:409-412, 1946. (*b*) Grossman, C. M., and Saward, E. W.: Homologous Serum Jaundice Following Administration of Commercial Pooled Plasma: Report of 8 Cases Including One Fatality, New Eng. J. Med. **234**:181-183, 1946. (*c*) Brightman, I. S., and Korns, R. F.: Homologous Serum Jaundice in Recipients of Pooled Plasma, J. A. M. A. **135**:268-272, 1947. (*d*) McGraw, Strumia, and Burns.[3]

the other hand, is usually reported as less than 1%.[5] In studies in which human volunteers have been used it has been shown that both the long-incubation-period hepatitis (serum hepatitis) and the short-incubation-period hepatitis (epidemic hepatitis) can be transmitted by means of whole blood or plasma.[6] From a practical point of view, however, short-incubation-period hepatitis seldom follows the use of pooled plasma. The explanation for this is not clear, but it is believed that the short-incubation-period hepatitis is a rather widespread disease; hence, in pooled plasma sufficient immune antibodies are present to counteract or neutralize the virus of epidemic hepatitis.

At the end of World War II pooled human plasma was stock-piled for use of the Armed Forces in the event of an emergency. Surplus plasma was distributed for use to civilian physicians and hospitals, accompanied by adequate warning regarding the risk of hepatitis.[7] Beginning in 1948 steps were initiated to irradiate plasma with ultraviolet light in order to inactivate the virus of hepatitis. This was first demonstrated to be possible by Oliphant and Hollaender,[8] and it was later demonstrated by Blanchard and his co-workers.[9] Although the risk of hepatitis with the use of this treated plasma was publicized to be minimal, occasional reports of hepatitis resulting from its use were seen.[10] In some instances these seemed to be related to the same lot of plasma and were believed to be due to inadequate irradiation. Until quite recently, therefore, much faith had been placed in ultraviolet irradiation of plasma for protection against the spread of hepatitis.

The outbreak of hostilities in Korea with the resulting inflow of casualties into hospitals in the United States made possible an opportunity to establish the incidence of hepatitis in a large number of recipients of whole blood and of pooled plasma, some of which had been irradiated with ultraviolet light.

MATERIAL AND METHODS

This study was conducted in three Army hospitals and included patients who were wounded between September 1950 and June 1951.[11] Specific wards were selected in each hospital, where

5. Neefe, J. R.: Viral hepatitis: Problems and Progress, Ann. Int. Med. **31**:857-870, 1949.

6. Havens, W. P., Jr.: Properties of the Etiologic Agent of Infectious Hepatitis, Proc. Soc. Exp. Biol. & Med. **58**:203-204, 1945. Neefe, J. R.; Stokes, J., Jr.; Reinhold, J. G., and Lukens, F. W. D.: Hepatitis Due to the Injection of Homologous Blood Products in Human Volunteers, J. Clin. Invest. **23**:836-855, 1944.

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8. Oliphant, J. W., and Hollaender, A.: Homologous Serum Jaundice: Experimental Inactivation of Etiologic Agent in Serum by Ultraviolet Irradiation, Pub. Health Rep. **61**:598-602, 1946.

9. Blanchard, M. C.; Stokes, J. Jr.; Hampil, B.; Wade, G. R., and Spizizen, J.: Methods of Protection Against Homologous Serum Hepatitis, II. The Inactivation of Hepatitis Virus SH with Ultraviolet Light, J. A. M. A. **138**:341-343, 1948.

10. Rosenthal, N.; Bassen, F. A., and Michael, S. R.: Probable Transmission of Viral Hepatitis by Ultraviolet Irradiated Plasma, J. A. M. A. **144**:244-226, 1950. Barnett, R. N.; Fox, R. A., and Snavely, J. G.: Hepatitis Following the Use of Irradiated Plasma, ibid. **144**: 226-228, 1950. James, G.; Korns, R. F., and Wright, A. W.: Homologous Serum Jaundice Associated with the Use of Irradiated Plasma, ibid. **144**:228-229, 1950. Greenlee, R. G.; Terrill, R. J., and Sloan, J. Q.: Homologous Serum Hepatitis After Transfusions of Blood and Ultra-Violet-Irradiated Plasma: Clinical Observations, Texas J. Med. **47**:831-835, 1951.

11. Colonel W. Stone, Colonel W. Willis, Colonel J. Knauer, Colonel F. Mowrey, Lieutenant Colonel F. Bauer, Lieutenant Colonel M. Guthrie, Major N. Calloway, Captain P. Teschan, and Captain R. Ettinger, Medical Corps, United States Army, assisted in this study.

wounded patients had been concentrated. Only those patients admitted thereafter to these specific wards or who were present on these wards at the start of the survey were included in the study. The patients followed were those who were injured since September 1950 and who had received blood or blood and plasma in the Far East Command. No patient was used in whom hepatitis developed prior to the start of this study, and no patient from any other ward of the hospital was included. Thus the material was strictly confined to a definite sample of patients, who were followed from 45 to 180 days after injury. Initial identifying data were gathered from each of these patients. This included the date of injury, the number of blood and plasma transfusions received, and the dates of these infusions. As a check against the history, the clinical record was consulted in each case. It was noted that the field medical records were, in the main, extremely reliable and correlated well with the patient's recollection of transfusions received. In certain instances differences were noted due to the fact that the patient had been unconscious when he received his transfusions or because he was evacuated so rapidly that he was unable to recall details of therapy received en route. When these differences occurred, only the recorded data were used for analysis.

At weekly intervals each patient included in the survey was carefully examined by a medical officer trained in the recognition of viral hepatitis. At that time the patient was closely questioned to determine whether he had had anorexia, nausea, vomiting, cigarette distaste, headache, upper right quadrant ache, dark urine, or pruritus in the preceding week. These data together with the results of a physical examination of skin and sclerae, liver size, and tenderness, and spleen size were recorded on a flow sheet. In two of the three hospitals a morning urine specimen was

Summary of Hepatitis Survey Data in Three Army Hospitals

	Plasma and Blood			Blood Alone		
		Hepatitis Cases			Hepatitis Cases	
	Recipients, No.	No.	%	Recipients, No.	No.	%
Hospital No. 1	176	38	21.6	262	6	2.3
Hospital No. 2	59	12	20.3	44	5	11.4
Hospital No. 3	20	6	30.0	26	1	3.8
Totals	255	56	21.9	332	12	3.6

taken from each patient twice weekly and examined for bilirubin[12] and urobilinogen.[13] When anything suggestive of liver disease was found in the history, physical examination, or the simple urine tests, blood was taken for liver function tests.

RESULTS

In the 10-month period covered by this survey a total of 587 casualties were followed. This figure includes 332 who received blood alone (average 5.6 units per patient) and 255 who received plasma and blood (average 1.4 units of plasma and 5.3 units whole blood per patient). The two groups were otherwise comparable in severity of wounding, general physical condition, and time of evacuation from the theater. In the majority of cases the only reason which determined whether a patient received plasma or blood was the local supply situation. In many instances whole blood was available as far forward as the battalion aid station, in which case it was used in preference to plasma. When supplies of whole blood were exhausted or otherwise not available, plasma was substituted.

12. Hawkinson, V.; Watson, C. J., and Turner, R. H.: A Modification of Harrison's Test for Bilirubin in the Urine, Especially Suited for Mass and Serial Usage, J. A. M. A. **129**:514-515, 1945.

13. Watson, C. J.; Schwartz, S.; Sborov, V. M., and Bertie, E.: Studies of Urobilinogen V: A Simple Method for the Quantitative Recording of the Ehrlich Reaction as Carried out with Urine and Feces, Am. J. Clin. Path. **14**:605, 1944.

A detailed summary of the results of this survey is shown in the Table. In 56, or 21.9%, of the wounded who received blood and plasma hepatitis with jaundice developed (total serum bilirubin 2 mg. per 100 cc. or more). In only 12, or 3.6%, of the casualties who received blood alone did hepatitis with jaundice develop. Figure 1 shows the month by month percentage of hepatitis, with a three-month floating mean for each of the two groups. With the exception of December 1950 (one casualty was studied and in him hepatitis developed) the percentage of hepa-

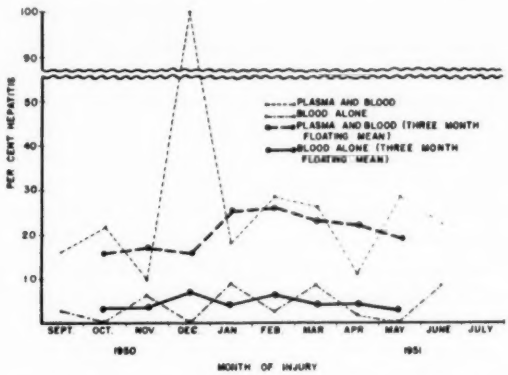
PER CENT HEPATITIS
PLASMA AND BLOOD
BLOOD ALONE
PLASMA AND BLOOD (THREE MONTH FLOATING MEAN)
BLOOD ALONE (THREE MONTH FLOATING MEAN)
SEPT. OCT. NOV. DEC. JAN. FEB. MAR. APR. MAY JUNE JULY
1950
1951
MONTH OF INJURY

Fig. 1.—Month by month percentage of hepatitis in Korean casualties.

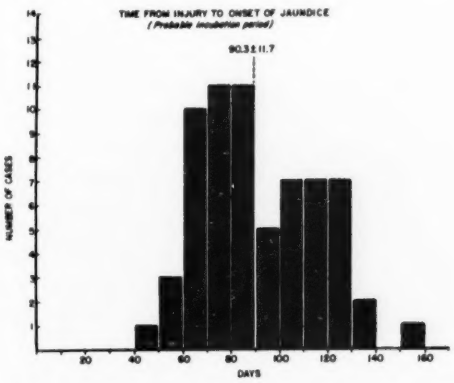

Fig. 2.—Probable incubation period of hepatitis in Korean casualties.

titis in those receiving blood and plasma varied from 10 to 28%. In those who received blood alone, on the other hand, the month by month percentage varied between 0 and 9%.

Of some interest in this study was the incubation period in the patients in whom hepatitis developed Since it was impossible to establish the exact time of exposure to the virus in the patients in whom jaundice did develop, the "probable incubation period" was used. This was defined as the number of days from the day of injury (the time of most infusions) to the first day of jaundice. The "probable incubation period" was found to vary from 44 to 151 days, with a mean of 90.3 ± 11.7

(Fig. 2). Only two patients showed a probable incubation period of less than 60 days. This was interpreted to indicate that the virus of the short-incubation-period hepatitis was probably not present in significant amounts in this group.

COMMENT

At the time of the outbreak of hostilities in Korea, in June of 1950, only unirradiated plasma was available in the Far East Command. One month later, however, plasma which had been reconstituted, pooled, irradiated, and lyophilized had reached the medical supply depots in Japan. It can be assumed that as the stocks of untreated plasma in the forward areas were exhausted they were replaced with ultraviolet-irradiated plasma. As late as March 1951, however, some unirradiated plasma was reported to be present in the using units. Because of this, the month by month incidence of hepatitis assumes great interest. It is believed that the cases of hepatitis occurring in those wounded during the first few months of this survey must reflect that resulting from the use of the untreated lots of plasma alone. A transition period would be expected to follow, after which only irradiated plasma was used, but this plasma was obtained from larger pools.[14] The predicted changeover did not result in a significant difference in the incidence of hepatitis. This suggests that all of the unirradiated plasma pools contained hepatitis virus and that the incidence figures seen merely show the number of persons in an exposed group in whom hepatitis with jaundice which can be detected with the method used in this survey will develop. Thus, no matter how many more donors are added to the original pool, a greater number of hepatitis cases will not result. This assumes, of course, that the ultraviolet irradiation has no effect upon the virus of hepatitis. In small groups of volunteers inoculated with known infected materials it has been shown that the usual incidence of hepatitis with jaundice is 15 to 50%,[15] a figure somewhat higher than that seen in this study. However, with the use of yellow fever vaccine containing human serum and a larger sample of recipients the highest incidence of jaundice with known contaminated material was about 9.5%,[16] but this represented a much smaller inoculum per patient. It is also possible that although results from the later months of this study reflect the use of larger size pools the ultraviolet irradiation affected the incidence somewhat so that the final figures are similar to those seen at the start of the survey. This seems unlikely, because of the recent demonstration by Oliphant and Murray that similar ultraviolet irradiation of known contaminated plasma will not reduce the incidence of hepatitis in human volunteers.[17]

The figures for hepatitis in this study that relate to the use of blood alone are higher than those previously reported and generally accepted. Due to the many difficulties encountered in a combat situation it is possible that some of these

14. If 50 to 100 untreated units, each containing material from 50 donors, were pooled for irradiation, the theoretical number of donors for each unit of treated plasma would be 2,500 to 5,000.

15. Oliphant, J. W.; Gilliam, A. G., and Larson, C. L.: Jaundice Following Administration of Human Serum, Pub. Health Rep. **58**:1233-1242, 1943. Footnote 6.

16. Sawyer, W. A.; Meyer, K. F.; Eaton, M. D.; Bauer, J. H.; Putnam, P., and Schwentker, F. F.: Jaundice in Army Personnel in the Western Region of the United States and Its Relation to Vaccination Against Yellow Fever, Am. J. Hyg. **39**:337-430, 1943.

17. Oliphant, J. W., and Murray: Personal communication to the authors.

patients may have received plasma as well as blood and that this was not recorded on the field medical record. It is also possible that because these casualties each received multiple whole blood infusions the risk of hepatitis was proportionally increased.

The lack of knowledge of the specific lots of pooled plasma used in these cases plus the use of multiple infusions of whole blood render exact formulation from these data impossible. It seems highly likely, however, that the figures previously available for the incidence of hepatitis following the use of pooled plasma are too low. The difference can be explained by the method of follow-up used. In most studies [18] this has consisted of a questionnaire sent to the patient or data obtained from a single interview of the recipient or his doctor several months after the transfusion was given. The accuracy of this type of study depends mainly upon the observation and the memory of the patient, both of which may be faulty. In contrast to this are the obvious advantages of the method of follow-up used in the present survey.

Finally, it is the opinion of the authors that this survey supplies sufficient information to state with reasonable certainty that irradiation with ultraviolet light as carried out in the plasma used for these casualties does not significantly affect the incidence of viral hepatitis among the recipients.

SUMMARY

In a careful follow-up study of 587 wounded soldiers it was found that in 21.9% of those who received blood and plasma hepatitis with jaundice developed. This was in contrast to an incidence of 3.6% among those who received blood alone.

The mean incubation period for this hepatitis was 90.3 ± 11.7 days, indicating that it probably all represented long-incubation-period hepatitis.

Although it is known that plasma irradiated with ultraviolet light was used during the latter period of this survey, a month by month breakdown of the incidence of hepatitis reflected no significant prevention of hepatitis by the irradiation.

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18. McGraw, Strumia, and Burns.[3] Footnote 4*b* and *c*.

OSTEOBLASTS AND OSTEOCLASTS IN BONE MARROW ASPIRATION

Previously Undescribed Cell Findings in Paget's Disease (Osteitis Deformans)

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SIR JAMES PAGET'S classic report [1] on osteitis deformans was followed by numerous investigations [2] which have established the protean clinical manifestations, the specific pathological picture, the biochemical alteration, and the roentgenographic abnormalities which characterize this condition whose causation still remains obscure. Although the clinical diagnosis is often made readily, at times there may be great difficulty in differentiating Paget's disease from other bone disorders, especially from osteoblastic cancer metastases.[3]

In this communication, hitherto undescribed cell findings in bone marrow aspirates will be reported. These cell findings were noted in eight consecutive cases of Paget's disease and consist of large mononuclear cells and giant multinucleated syncytial forms, both of which have unique morphological characteristics. The detailed cytology of these cells and their significance will be presented below.

INITIAL OBSERVATIONS

Early in 1952, an iliac bone marrow smear from a patient (Case 1) with suspected pernicious anemia was examined by us. It lacked normal marrow elements but contained several clumps of unusual large cells, which were reported as "reticulum cells, possibly neoplastic." However, they could not be identified with any of the neo-

From the Division of Neoplastic Diseases and the Medical Division, Montefiore Hospital.

1. Paget, J.: On a Form of Chronic Inflammation of Bones (Osteitis Deformans), Medico-Chirurg. Trans. London **60**:37, 1877.

2. Only few out of very many bibliographical references can be given here. (*a*) Schmorl, G.: Über Ostitis deformans Paget, Virchows Arch. path. Anat. **283**:694-737, 1932. (*b*) Gutman, A. B., and Kasabach, H. H.: Paget Disease (Osteitis Deformans): Analysis of 116 Cases, Am. J. M. Sc. **191**:361, 1936. (*c*) Brailsford, J. F.: Paget's Diseases of Bone: Its Frequency, Diagnosis and Complications, Brit. J. Radiol. **11**:507-32, 1938. (*d*) Kay, H. D.: Plasma Phosphatase in Osteitis Deformans and Other Diseases of Bone, Brit. J. Exper. Path. **10**:253-256, 1929. (*e*) Gutman, A. B.; Tyson, T. L., and Gutman, E. B.: Serum Calcium, Inorganic Phosphorus and Phosphatase Activity in Hyperparathyroidism, Paget's Disease, Multiple Myeloma and Neoplastic Disease of the Bones, Arch. Int. Med. **57**:379, 1936. (*f*) Jaffe, H. L.: Paget's Disease of Bone, Arch. Path. **15**:83, 1933. (*g*) Snapper, I.: Medical Clinics on Bone Diseases, Ed. 2, New York, Interscience Publishers, Inc., 1951.

3. Sutherland, C. B.: Differentiation of Osteitis Deformans and Osteoplastic Metastatic Carcinoma, Radiology **10**:150, 1928. Brailsford, J. F.: The Radiology of Bones and Joints, Baltimore, Williams & Wilkins Company, 1934.

plastic cell types previously described elsewhere.[4] When it was learned that the patient had well-documented osteitis deformans, we considered that these cells might indicate the sarcomatous change which sometimes occurs in this disease.[5]

A year later, a routine iliac marrow aspiration in another patient with Paget's disease showed the same peculiar cells. Review of the first case revealed that in the interim no clinical or roentgenographic change had occurred and that the same cells could still be aspirated from the ilium.

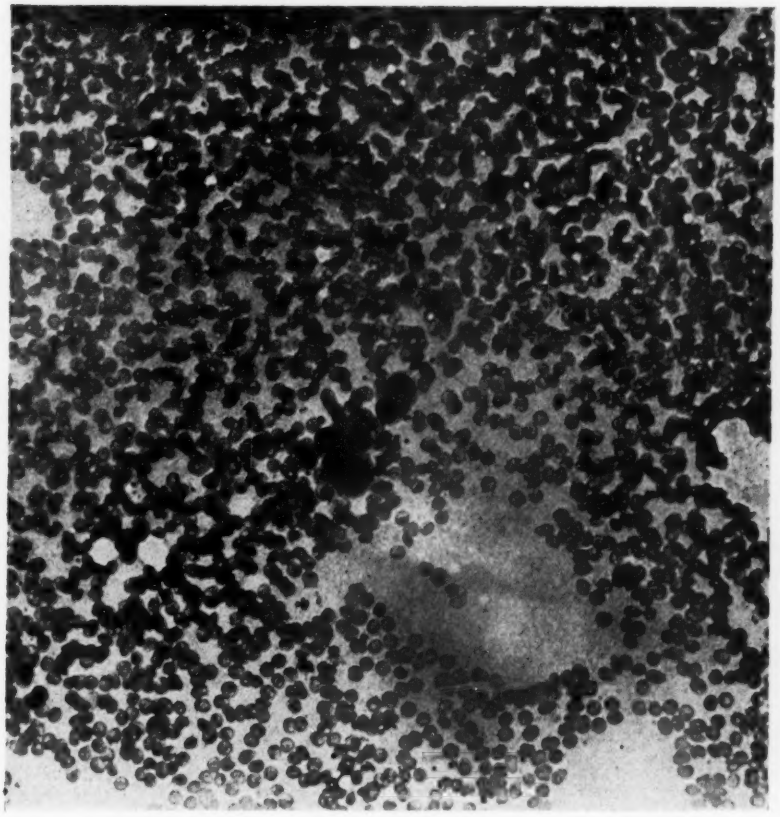

Fig. 1 (Case 4).—Iliac aspiration, showing clusters of individual mononuclear cells in otherwise aplastic marrow; × 260.

It was then postulated that these cells might be characteristically found in bone marrow aspirates from areas of osteitis deformans, and, accordingly, bone marrow studies were performed in five additional cases of osteitis deformans. In each case

4. Rubinstein, M. A., and Smelin, A.: Neoplastic Cells in Bone Marrow Aspiration, Acta Haemat. **5**:292, 1951.

5. Bird, C. E.: Sarcoma Complicating Paget's Disease of the Bone: Report of 9 Cases; 5 with Pathologic Verification, Arch. Surg. **14**:1187, 1927. Camp, J. D.: Sarcoma Complicating Osteitis Deformans, Radiology **5**:495, 1925. Coley, B. L., and Sharp, G. S.: Paget's Disease: A Predisposing Factor in Osteogenic Sarcoma, Arch. Surg. **23**:918, 1931.

aspiration was done from iliac bone that was roentgenologically involved with the disease, and the typical cells were recovered in all instances. An eighth case (Case 3) was acquired when one of us (A. S.) recalled having seen morphologically similar cells in the iliac marrow of a patient studied in 1951; review of the chart and slides confirmed the existence of Paget's disease and the characteristic cells, respectively.

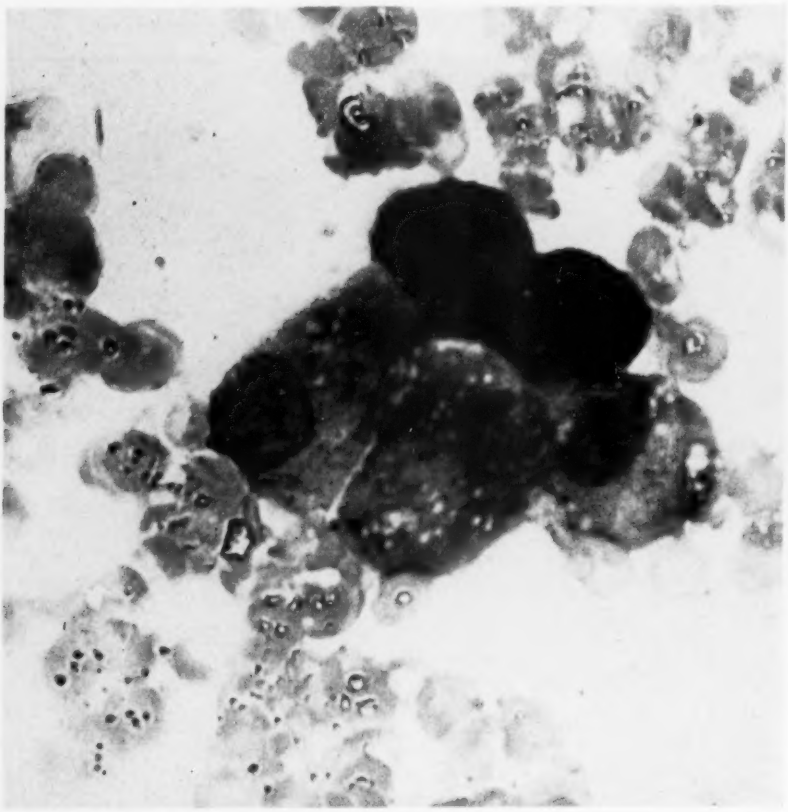

Fig. 2 (Case 1).—Clumps of individual cells showing vacuolated appearance of cytoplasm.

DESCRIPTION OF CELLS

Two unique cytologic elements may be distinguished in bone marrow aspirates from areas of osteitis deformans: (1) individual mononuclear cells occurring singly and in clumps and (2) multinucleated syncytial forms.

Individual Mononuclear Cells (Figs. 1, 2, 3, 4, and 5).—These elements can be easily recognized with the low-power objective. They are large (25 to 50 μ in the greatest diameter), ovoid in shape, and generally have hazy ill-defined cytoplasmic borders. The nucleus is round and has a diameter of 12 to 16 μ. It is characteristically located eccentrically and frequently appears to have been partially extruded from the cytoplasm (Fig. 4). With Wright's stain the nucleus takes on a lilac to purple hue and contains one or several clear blue nucleoli. The cytoplasm stains gray-blue

to deep blue and often has a stippled or ground-glass appearance. It frequently contains a central clear zone, around which a few azurophilic granules may be found. The staining properties of the cytoplasm are not uniform, and the impression of vacuolization may be created (Fig. 2). The cytoplasm : nucleus ratio is about 3 : 1, considerably greater than for most tumor cells.

The individual cells may appear singly scattered through the smear or in clumps of two or more cells. In contradistinction to the syncytial cell forms to be

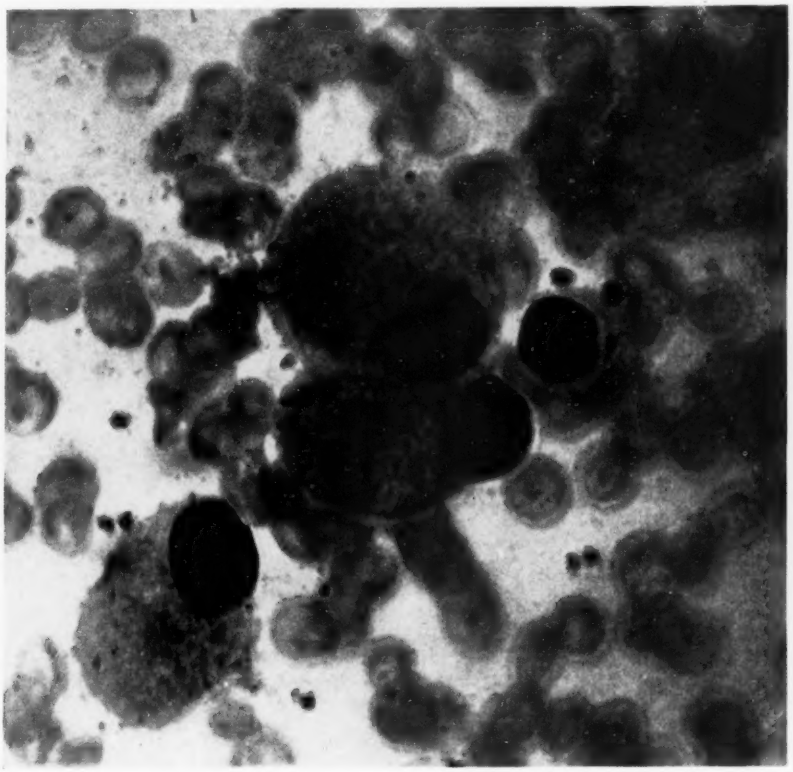

Fig. 3 (Case 4).—Several mononuclear cells showing eccentric nuclei and cytoplasmic granulation.

described below, clumps of individual cells always contain independent cytoplasmic borders. Originally we described these cells as "reticulum-plasmacytoid" elements and to those unfamiliar with their appearance they may, at first glance, seem to resemble plasma cells, reticulum cells, or, especially when found in clumps, tumor cells. With but little experience, however, the morphological differentiation is simple.

The number of these cells in the aspirate varies greatly in individual cases, ranging from 20 or more single or clumped cells per high-power field to only a few cells in an entire smear. As a rule, hemopoietically aplastic smears contain large

numbers of these cells, while active marrows contain few. In addition to iliac aspiration, in three cases sternal and in a fourth case vertebral aspiration was performed and examination showed essentially normal hemopoietic activity and none of the characteristic cells; these bones were normally resistant to needle puncture and were not involved with osteitis deformans roentgenographically.

Syncytial Cell Forms (Figs. 6 and 7).—These multinucleated elements were recognized in three cases (Cases 1, 4, and 5). They may reach huge sizes (over

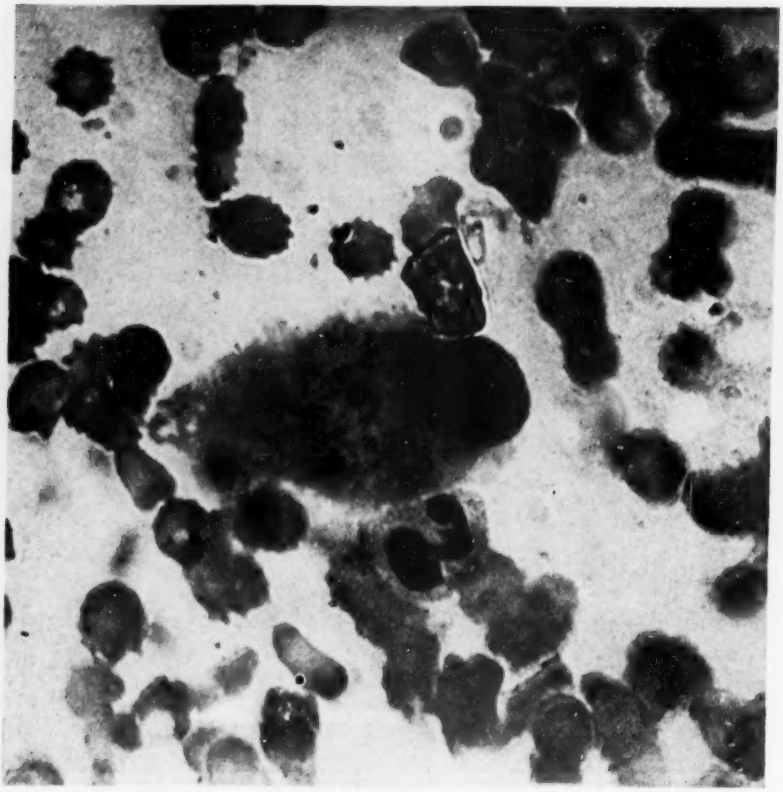

Fig. 4 (Case 6).—Single mononuclear cell. Note "extruded" nucleus with nucleoli, central clear zone, and fuzzy cytoplasmic borders; × 1,100.

200 μ) and occasionally contain as many as 100 nuclei, but smaller forms containing only a few nuclei are frequently seen. It is possible that the latter are portions torn from the former giant cells in the process of making the smear. The nuclei, which are distributed haphazardly throughout the syncytium and are sometimes arranged in rouleaux, are of uniform size and appearance and often contain one or several nucleoli; they are morphologically not dissimilar to the nuclei of the single mononuclear cells described above. The cytoplasmic mass is much less abundant in relation to the nuclear mass in the syncytial than in the mononuclear forms. The cytoplasm appears gray to blue with Wright's stain, has a ground-glass or hazy

quality, and may contain azurophilic granules much like the cytoplasm of the mononuclear cell. The syncytial cells are readily differentiated from megakaryocytes, the only normal marrow elements which approach them in size.

REPORT OF CASES

CASE 1.—M. C., a 63-year-old woman, has been hospitalized for many years because of a neurologic disorder, probably multiple sclerosis. Repeated bone surveys have shown roentgen manifestations of Paget's disease limited to the pelvis (Fig. 8*A*). The blood alkaline phosphatase

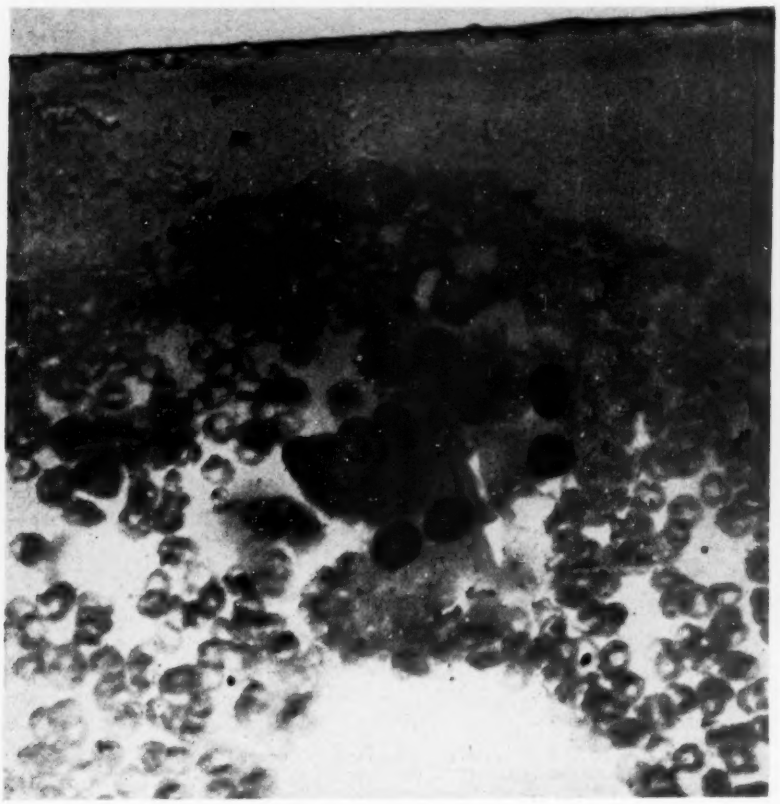

Fig. 5 (Case 3).—Clumps of mononuclear cells. Note individuality of cell borders.

was elevated and has ranged between 8 and 15 Bodansky units. The levels of serum calcium phosphorus, albumin, and globulin and results of liver function studies have been normal. The red and white cell counts have remained essentially normal.

A left iliac bone marrow aspiration was done in February 1952 to help rule out subacute combined degeneration. It showed hemopoietic aplasia and a number of single and clumped unique mononuclear cells (Fig. 2). During the following year five bone marrow aspirations were performed: two, from the left iliac crest, confirmed the presence of destructive mononuclear cells and demonstrated several giant syncytial cells; one, from the right iliac crest, showed less aplastic marrow and contained a few mononuclear and syncytial forms, and two, from the sternum, showed hyperactive but essentially normal marrow.

The patient's clinical condition has remained unchanged, and her Paget's disease is asymptomatic.

CASE 2.—H. B., a 61-year-old man, has, over the past 10 years, suffered pathological fractures of the right tibia, right radius, and spine. Roentgenograms of the skeletal system show advanced osteitis deformans of the spine, pelvis, right radius, and tibia (Fig. 8*B*). Biopsy of the vertebral body in 1949 was pathognomonic for this condition. Blood alkaline phosphatase has ranged

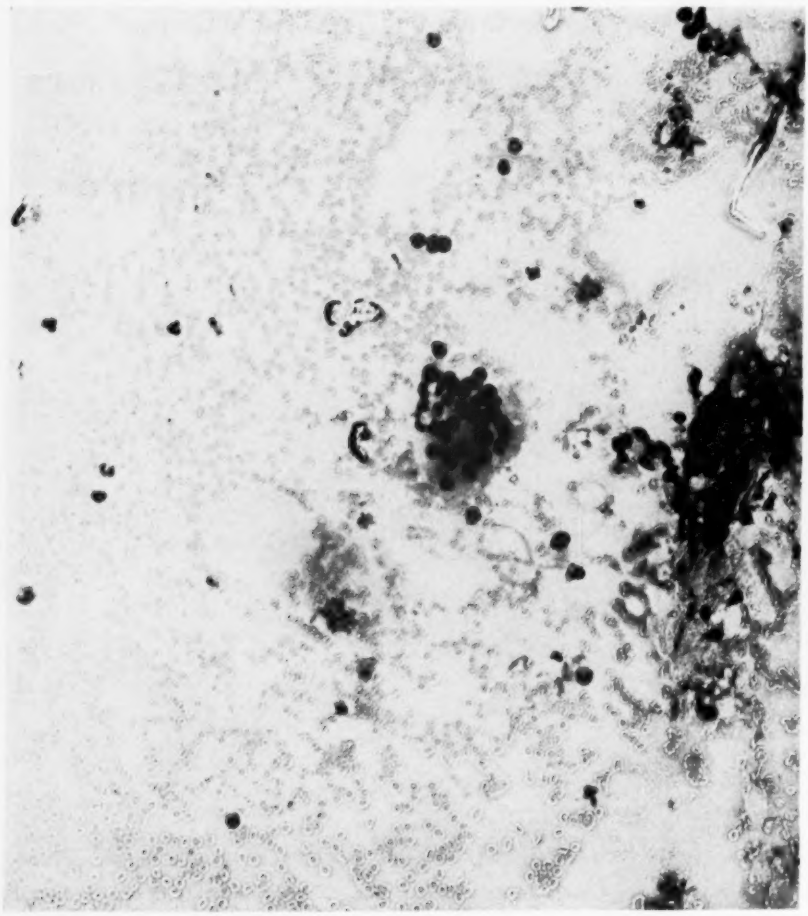

Fig. 6 (Case 4).—Low-power view of a giant syncytial form; × 180.

between 29 and 50 Bodansky units. Blood calcium and phosphorus and hemograms are essentially normal.

Iliac bone marrow aspirations in January 1953 revealed the absence of normal marrow elements and the presence of many of the characteristic cells, both singly and in clumps (Fig. 9). No syncytial forms were observed. A sternal marrow aspirate was hyperplastic and of normal composition.

CASE 3.—J. W., a 75-year-old white man with hypertension, was hospitalized in 1951 for congestive heart failure. He had the residual hemiplegia of a cerebral thrombosis that had

occurred a year before. Roentgenograms showed osteitis deformans of the pelvis and skull (Fig. 10). Blood alkaline phosphatase was 4.1 Bodansky units on a single determination. Hemograms and blood calcium and phosphorus were normal.

In August 1951 a left iliac aspirate showed moderately active marrow containing numerous large mononuclear cells both singly and in clumps.[5] At that time these were considered to be "tumor cells" from an unknown primary site. Shortly thereafter, the patient died from cardiac causes and autopsy revealed generalized arteriosclerosis and hypertensive-arteriosclerotic heart

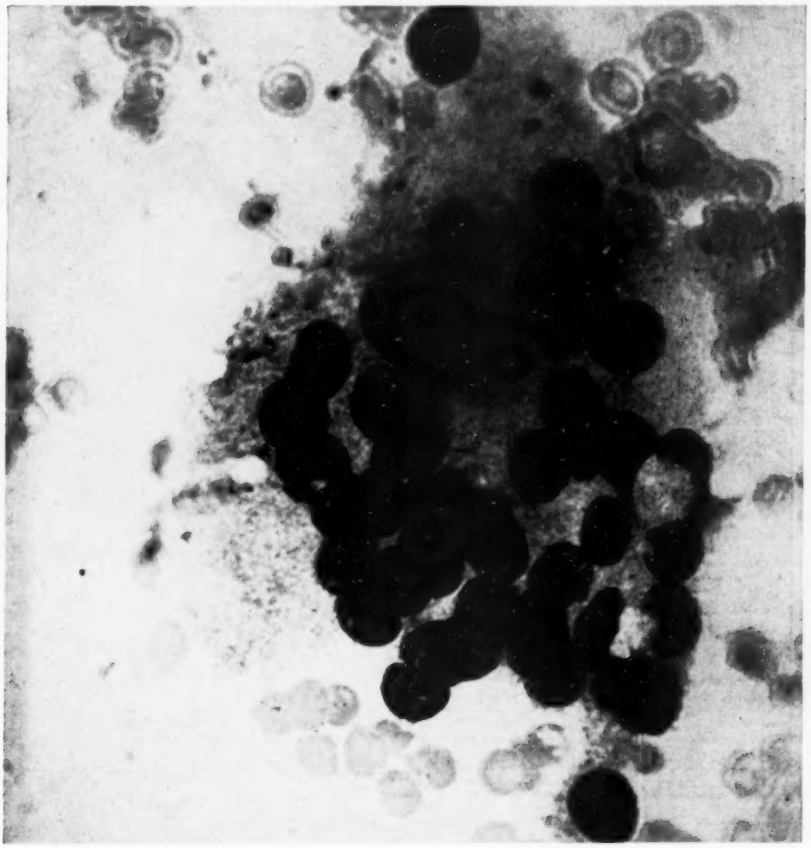

Fig. 7 (Case 4).—High-power view of the syncytial cells shown in Figure 6; × 770.

disease but no evidence of cancer. When, in retrospect, the bone marrow slides were reviewed in 1953, the previously considered "tumor cells" were found to be identical with cells described in this paper. No syncytial forms were noted.

CASE 4.[6]—Because of a two-year history of low back pain and sudden onset of cord compression, this 46-year-old man H. I. was hospitalized in January 1953. Roentgenograms showed Paget's disease involving the pelvis, lumbosacral spine, and ribs. Blood alkaline phosphatase was 18.5 Bodansky units. The hemogram, blood calcium, and phosphorus were essentially normal.

6. Permission to do bone marrow studies and to present this case was granted by Dr. Ralph Greenberg.

Decompressive laminectomies were performed at the first lumbar and eighth thoracic vertebrae with good results. Bone typical of osteitis deformans was noted at operation, and the diagnosis was confirmed histologically.

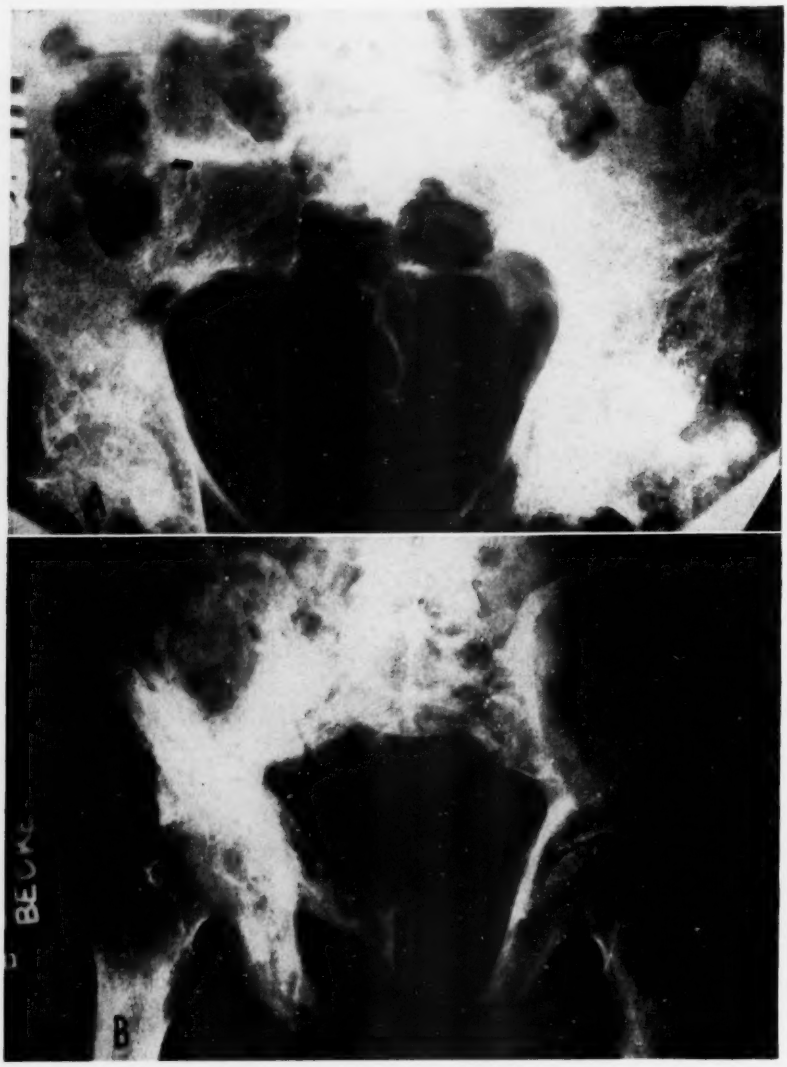

Fig. 8—*A*, roentgenogram showing osteitis deformans of pelvis in Case 1. *B*, marked osteitis deformans of spine and right pelvis in Case 2.

Postoperatively, bone marrow aspirations were performed from the sternum and both iliac crests. The left iliac crest was abnormally soft, and a marrow smear was hypoplastic, with numerous of the typical mononuclear (Figs. 1 and 3) and giant syncytial forms present (Figs. 6 and 7). A few of the mononuclear cells were seen in marrow from the right iliac crest, but none were obtained from the sternum.

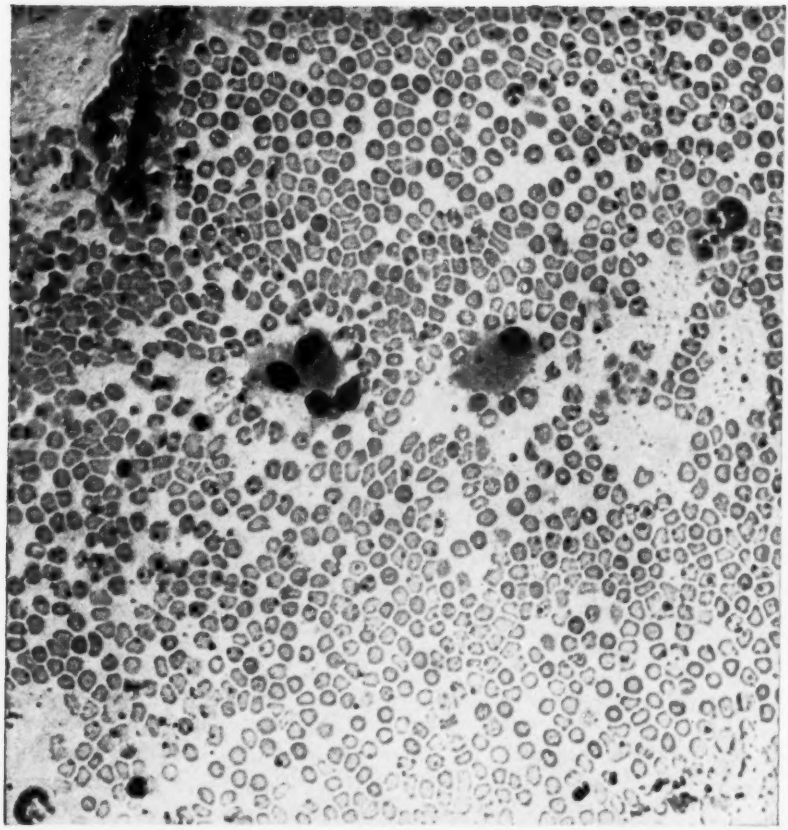

Fig. 9 (Case 2).—Several single mononuclear cells from iliac marrow; × 310.

Fig. 10 (Case 3).—Paget's disease of pelvis.

CASE 5.[7]—Because of crippling Paget's disease, this elderly kyphoscoliotic dwarf (A. L.) has been hospitalized for over 10 years. His main symptomatology is referable to cranial and spinal involvement. Roentgenograms show osteitis deformans involving the skull, pelvis, spine, both tibias, and the left femur and humerus. Blood calcium and phosphorus have been normal, and alkaline phosphatase has ranged from 41 to 50 King-Armstrong units.

A left iliac crest aspiration demonstrated soft bone and revealed aplastic dilute marrow containing the typical mononuclear cells both singly (Fig. 4) and in clumps. None of the syncytial forms were noted.

CASE 7.[7]—This chronically ill 73-year-old man (C. T.) suffers from bone disease, arteriosclerotic heart disease, and a duodenal ulcer. Roentgenograms were interpreted as showing osteoporosis circumscripts and typical osteitis deformans in the skull, pelvis, femora, and right shoulder. Blood calcium was 12.2 and 12.0 mg., phosphorus was 2.1 and 2.2 mg., and alkaline phosphatase was 58.5 and 100 King-Armstrong units. Clinicians in charge of the case consider the diagnosis to be Paget's disease although primary hyperparathyroidism has not been completely ruled out.

Needle aspiration from the soft left iliac crest obtained dilute hypoplastic marrow containing the typical cells, singly and in clumps, in small numbers. The syncytial forms were absent.

CASE 8.—This elderly woman (M. C.) with the typical roentgen manifestations of advanced osteitis deformans has a pathological fracture of the right femur. She also suffers from hypertensive and arteriosclerotic heart disease. The blood calcium and phosphorus are normal, and alkaline phosphatase is 53 King-Armstrong units.

A right iliac bone marrow aspirate revealed normal cellularity and rare mononuclear cells having the same appearance as those seen in the previous cases. Syncytial forms were absent

COMMENT

An extensive review of the literature concerning osteitis deformans reveals that the bone marrow has been infrequently studied and that unusual cell findings have not previously been reported.[8] The failure to recognize the cells described in this report previously may be attributed to the following causes: 1. Sternal marrow aspiration has been the usual procedure elsewhere. Paget's disease rarely involves the sternum but involves the pelvis most frequently.[9] The iliac crest is the usual site of bone marrow aspiration at this hospital.[10] 2. The unusual cells may have been observed but discounted as reticulum cells, plasma cells, smudged cells, etc. 3. The aplastic marrow, in which these cells usually occur, may have been discarded as an unsatisfactory specimen without being carefully studied.

Since the characteristic cellular elements were found in all cases of Paget's disease when aspiration was made at the site of bone involvement and were absent from uninvolved areas, the confirmatory diagnostic importance of bone marrow aspiration in this disease is quite evident. However, these cells cannot be considered pathognomonic of osteitis deformans. Indeed we have recovered them in other conditions, as noted below. There is no reason to expect that cells pathognomonic of Paget's disease should be found in bone marrow aspirates, since, pathologically, it is the

7. Permission and arrangements to study and present this case, from the Goldwater Memorial Hospital, were provided by Drs. H. Kaden and H. Spencer.

8. Rosenkrantz, J. A.; Wolf, J., and Kaicher, J. J.: Paget's Disease (Osteitis Deformans): Review of 111 Cases, A. M. A. Arch. Int. Med. **90**:610, 1952.

9. Dickson, D. D.; Camp, J. D., and Ghormley, R. K.: Osteitis Deformans: Paget's Disease, Radiology **44**:449, 1945.

10. Rubinstein, M. A.: Aspiration of Bone Marrow from the Iliac Crest: Comparison of Iliac Crest and Sternal Bone Marrow Studies, J. A. M. A. **137**:1281, 1948.

deranged architecture of involved bone, and not the cytology, that is diagnostic. Correlation of the cytologic findings presented in this report with the morbid anatomy of osteitis deformans might therefore be illuminating.

Osteitis deformans is characterized by markedly accelerated bone resorption and bone repair. There is evidence that the initial lesion is bone destruction produced by an unknown localized factor,[11] and in this phase numerous osteoclasts are seen. The involved bone becomes more susceptible to stresses and strains; osteoblasts multiply in number and activity, as is reflected by a rising serum alkaline phosphatase. In the areas most subject to stress and strain (pelvis, spine, femora) bone repair usually occurs almost simultaneously with bone destruction, resulting in the characteristic "mosaic structure" (Schmorl [2a]) due to the irregular bizarre arrangement of the cement lines within the trabeculae. In areas less subject to stress (skull) bone repair may lag behind bone destruction, resulting in osteoporosis circumscripta. The usual histology of involved bone includes marked fibrosis, and the thickened and distorted bone trabeculae are lined by increased numbers of osteoblasts and osteoclasts.

In correlating this histologic picture with the cell forms described in this paper the first thought would be that the mononuclear cells are osteoblasts and the multinucleated syncytial forms are osteoclasts. Such identification is supported by studies of the histologic appearance of growing bone.[12] The individual cells found on aspiration correspond to tissue cells described by histologists as osteoblasts, while the multinucleated forms closely resemble the syncytial elements described as osteoclasts.[13] Comparative cytologic and cytochemical studies on material from bone marrow aspirates and from bone biopsy obtained from the same area of osteitis deformans are in progress here.

A search is also being conducted for the unique mononuclear and syncytial cells in conditions other than Paget's disease which are known to be accompanied by increased osteoblastic and osteoclastic activity. Physiologically such increased activity occurs in the growth zones of infants' bone and at the site of fracture undergoing repair. Pathologically, it may occur in rickets, primary and secondary hyperparathyroidism, and in association with certain blood dyscrasias in osteoblastic malignant disease of bone.

Review of the literature reveals two independent reports [13] in which mononuclear and syncytial forms closely resembling those described in this paper were recovered in bone marrow aspirated from the growth zones of the long bones of normal infants and from rachitic bone.

We have observed a few of the mononuclear cells in the marrow of a patient with osteoblastic metastases secondary to carcinoma of the breast; a review of over 20 similar cases of osteoblastic cancer (the bone marrow smear in each case containing typical clumps of tumor cells) was negative for the cells described in this paper. We

11. Albright, F., and Reifenstein, E. C., Jr.: The Parathyroid Glands and Metabolic Bone Disease, Baltimore, Williams & Wilkins Company, 1948, p. 249.

12. Esser, M.: Osteoblasten und Osteoklasten in Knochenmarkaustrichen, Helvet. med. acta **12**:265, 1945.

13. Cazal, P., and Bertrand, L.: Les cellules de la zone ostéoïde du cartilage de conjugaison dans le myélogramme tibial de l'enfant (et plus particulièrement de l'enfant rachitique), Rev. hémat. **1**:293, 1946. Esser.[12]

have also noted a few of the mononuclear cells in one case of osteosclerosis secondary to myelogenous leukemia and in one case of anemia (possibly Cooley's) in a child. In conditions other than Paget's disease, we have found large numbers of the mononuclear cells and also syncytial cells in only one case. This was in a young man with uremia and secondary hyperparathyroidism. In one case of probable primary hyperparathyroidism studied the unique cells were found. These findings will be the subject of a separate publication.

SUMMARY

Two cell types previously undescribed in bone marrow aspirated from patients with osteitis deformans were found (either independently or in association) in eight consecutive cases of this disease. The cells were present only in aspirates from involved bone.

Other conditions in which one or both cells were found are noted.

The morphologic characteristics of the two cells, their incidence, and their relation to other bone marrow elements are presented.

Evidence and a rationale are presented which identify these cells, a mononuclear and multinucleated form, with the osteoblast and osteoclast, respectively.

The finding of these cells in bone marrow aspirates may be of value in providing confirmatory evidence or leading to suspicion of Paget's disease and certain other conditions. The cells should not be confused with tumor cells.

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FAMILIAL CLUBBING OF FINGERS AND TOES

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THE CLUBBING of the digits described by Hippocrates in the fifth century B. C. was associated with one of the progressive morbid states that may present this physical finding, i. e. empyema. Other maladies which may produce clubbing include chronic suppurative lung disease, cyanotic congenital heart disease, subacute bacterial endocarditis, liver cirrhosis, and inflammatory or neoplastic disorders of the gastrointestinal tract. But not all clubbing of the fingers or toes portends serious organic dysfunction. Clubbing may be present as an hereditary anomaly in selected families.[1] When this anomaly is observed in a presumably healthy person, inquiry into the duration of the abnormality and the possible familial distribution may be rewarding. At least this was our experience.

Although the familial and acquired forms of clubbing have a similar appearance superficially, the former variety occasionally may involve only one or two fingers symmetrically. The rule, however, is symmetrical involvement of all digits. The characteristic presumably is transmitted as a simple Mendelian dominant.[2] Ebstein,[3] to the contrary, submitted certain data from two pedigrees which suggested its transmission as an irregular dominant.

The "B" family in western New York, stigmatized by familial clubbing, first came to our attention approximately five years ago. Marked symmetrical clubbing of the fingers and toes was observed in a member of the second generation, who was admitted to the Buffalo General Hospital with a presumptive diagnosis of heart disease. Mild dyspnea on exertion was the chief complaint, and clubbing of the fingers and toes was an arresting physical finding. The examination revealed no evidence of organic disease of the internal systems. The suspect was not cyanotic. Roentgenographic study of the chest and long bones revealed no abnormalities. Functional studies of the heart, lungs, liver, and gastrointestinal tract revealed no

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The Buffalo Chapter of the Arthritis and Rheumatism Foundation (a Community Chest activity) has contributed to the support of the researches on joint disorders conducted by the department.

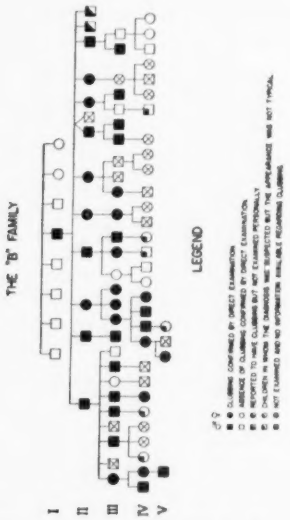
1. Fraentzael, O.: Deutsche med. Wchnschr. **14**:651, 1888. Freytag, A.: Über die Trommelschlägelfinger und Knochveränderungen bei chronischen Lungen- und Herzkrankheiten. Bonn, Hauptmann, 1891. Mangelsdorf, J.: Wein. med. Wchnschr. **35**:361, 1885.

2. Neurath, R.: Wein. klin. Wchnschr. **45**:1210, 1932.

3. Ebstein, E.: Dermat. Wchnschr. **68**:113, 1919. Ebstein, E., in Heller, J.: Die Krankheiten der Nägel, Berlin, Springer-Verlag, 1927.

demonstrable disturbance. Inquiry disclosed that the clubbing had been present for as long as the patient could recall and that other members of the family were similarly afflicted in the absence of clinical disease. A medical-social survey was then made by one of us (W. M.).

A systematic investigation of each living member of the family who was sympathetic to the study revealed that a majority exhibited this inherited trait. To all outward appearances, and, in some instances as evidenced by complete physical examination, each was free from organic disease. Random sampling of roentgenograms of the chest, hands, and wrists failed to uncover any well-developed or incipient heart or pulmonary disease or the presence of hypertrophic pulmonary osteoarthropathy.



Genealogical tree of "B" family.

For the purpose of the study the family consisted of almost 75 persons, whose ages at the time of the initial examination ranged from 9 days to 72 years. Four generations are reported among the living members. The paternal parent of the line was never seen, but photographs and descriptions of his hands have convinced us that it is acceptable to include him in the family tree as an affected member. Thus, in fact, five generations are covered.

The genealogical results of the survey are shown in the Figure. Each member of the second generation was seen, except three. One was a dead twin. The two indicated on the extreme right of the figure were not seen but were reported to have clubbing. Thus, the percentage of clubbing of the second generation is almost 100%. The members of the following generations were not studied as completely, but well-developed clubbing was readily recognized in many of them.

If it is assumed that the original parent was a homozygos with a normal wife, the characteristic behaves as a simple Mendelian dominant. It does not appear to be sex linked and is not sex influenced. It passes through males and females, and

no generations are skipped. The first parent died in his 80's and none of the family has had any serious illnesses, at least none which kept him from work or school. It was not possible to determine whether intermarriage had occurred in this family.

Clubbing in our series was called positive when the changes which are supposed to appear first in the condition were present. There is an obliteration of the normal angle between the plane of the nail root and that of the bone of the distal phalanx. This angle is approximately 15 degrees in the person without clubbing. The angle becomes obliterated by thickening of the fibroelastic tissue of the nail bed and coincident elevation at the base of the nail. A heaped-up thickened eponychium and paronychium are common. The nails become rounded and shiny, and there is increased resiliency of the base of the nail so that an easy forward and backward rocking effect is produced. The ends of the fingers are warm and red, and the nails grow more rapidly. The familiar full-blown picture of curved nails and drumstick terminal phalanges offered no problem.[4] In such instances x-ray studies show splaying of the phalanges.[5]

The time of onset of clubbing is not always noted by the person himself. It is not an easy task for a lay person to recognize minimal degrees of change. Futhermore, in simple clubbing, either acquired or inherited, there may be no local symptoms and development is usually so gradual that the afflicted person is frequently not aware of it. It has been presumed in the case of familial clubbing that the condition is present at birth. A number of infants have been observed in the "B" family, and the difficulty in recognizing the condition has been outstanding in each of the children. We believe that the youngest child in whom we could be fairly certain that clubbing existed was 2 years old. Babies' fingers have slightly bulbous ends normally, and the nail changes have not been prominent. Most members of the family were not particularly aware of the finger changes until they were pointed out. This may indicate that the changes were present for a long time or developed very slowly. The most striking observation was the fact that the condition was more pronounced in older persons.[6] If the family members over 50 had clubbing, they had it to a marked degree. It would appear that the condition is not a static one, as has been suggested, but that there is some physiologic change associated with advancing years that makes the condition more manifest. This is perhaps consistent with the observations made on other hereditary traits which do not become apparent clinically until later years. Why development of the inherited characteristic is sometimes delayed and why the acquired type may wax and wane probably cannot be answered until the pathogenesis of acquired clubbing in known.

It has been postulated generally that the condition is the result of arterial anoxia, but this theory fails to explain the condition when diminution of the arterial oxygen saturation in the large vessels cannot be demonstrated. Recently Mauer[7] has postulated that for certain physical-chemical reasons, and possibly anatomical ones as well, oxygenation of the tissue in the distal phalanges is deficient, thus accounting for clubbing. Since the degree of tissue oxygenation cannot be measured satisfac-

4. Horsfall, F. L., Jr.: Canad. M. A. J. **34**:145, 1936. Kayne, G. G.: Proc. Roy. Soc. Med. **26**:270, 1933. Seaton, D. R.: Brit. M. J. **1**:614, 1938.

5. Witherspoon, J. T.: Arch. Int. Med. **57**:18, 1936.

6. Lewy, E.: Med. Klin. **17**: 845, 1921.

7. Mauer, E. F.: Am. Heart J. **34**:852, 1947.

torily at the present time, this explanation must remain a postulate. Mendlowitz [8] determined the blood flow and the pressure gradient in one patient with asymmetrical familial clubbing. There was no essential difference in the functions measured between the clubbed and the nonclubbed digits.

SUMMARY

A large family has been observed which comprises five generations. A majority of the members exhibit clubbing of the fingers, sometimes known as "Hippocratic nails," without evidence of systemic disease. The family pedigree suggests that the trait is hereditary and that it behaves in the manner of a simple Mendelian dominant without sex linkage or influence. The observations on the family accent the fact that clubbing need not necessarily be a diagnostic sign of systemic disease and that in this form it is associated with no threat to a long and comfortable life.

8. Mendlowitz, M.: J. Clin. Invest. **20**:113, 1941

Progress in Internal Medicine

AORTIC ARCH SYNDROMES

Diminished or Absent Pulses in Arteries Arising from Arch of Aorta

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IN THE case of absent or diminished pulses in the arms and neck the clinician is presented with a most dramatic physical finding. Although the observation itself is elemental, the interpretation may be difficult.

Anisosphygmia, "pulsus incongruens," and "pulsus differens" [1] are terms which have been applied to pulse abnormalities of this general type. "Pulseless disease" is another name applied to some of these abnormalities.[2] Fortunately no eponyms have come into particular usage in connection with these cases, although the type of disease due apparently to arteritis is called Takayasu's disease in Japan.[2b]

It is our purpose to present cases in which the seat of the disorder is near the origin of the great vessels from the arch of the aorta. Included are various combinations of stenosis and obliteration of various branches of the aortic arch resulting from various causes. This general clinical picture may be referred to, as first suggested by Frøvig,[3] as the aortic arch syndrome(s). Not included are instances in which the arterial disease responsible is located at a distance from the arch, although in the differential diagnosis of the arch syndromes many of these other vascular disorders must be considered.

This review is based on an analysis of over 100 cases of this syndrome, of which 35 have not been previously reported.

CLINICAL PICTURE

Characteristically in the aortic arch syndromes the pulses in the arm become impalpable before the blood pressure becomes completely unobtainable by the Korotkoff sounds. For instance, pulses may be impalpable, yet a few sounds may be heard at pressures between 80 and 75 mm. Hg when the blood pressure is determined in the usual way. If local blood pressure beyond an obstruction is measured

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1. Symonds, C. P.: Two Cases of Thrombosis of Subclavian Artery: With Contralateral Hemiplegia of Sudden Onset, Probably Embolic, Brain **50**:259, 1927.

2. (*a*) Shimizu, K., and Sano, K.: Pulseless Disease, J. Neuropath. & Clin. Neurol. **1**:37, 1951. (*b*) Caccamise, W. C., and Whitman, J. F.: Pulseless Disease: A Preliminary Case Report, Am. Heart J. **44**:629, 1952.

3. Frøvig, A. G.: Bilateral Obliteration of the Common Carotid Artery, Acta psychiat. et neurol., Supp. 39, 1946.

by intra-arterial techniques,[4] one finds greatly reduced pulse pressure but often only slight reduction of mean arterial pressure. The paucity of clinical evidences of ischemia of the arms may be a reflection of the distinction between absence of pulses and absence (or serious reduction) of blood flow. In obstruction at the aortic arch the normal pressure oscillations in the arteries of the arm are damped but a steady mean arterial pressure is maintained. The discrepancies between pulse and blood flow are well demonstrated by direct intra-arterial pressure recordings and plethysmography in cases of left subclavian artery involvement and coarctation of the aorta.[5]

After no Korotkoff sounds are audible systolic blood pressure in the arm can be approximated, as pointed out by Deneke[6] and by others,[7] by a modification of the Gaertner method.[8] The arm is raised above the head (i. e., above the level of the heart), and the cuff is inflated. The arm is lowered, and the pressure in the cuff slowly released. The pressure at the time that a flush first appears in the hand and forearm is taken as an approximation of mean arterial pressure in the arm.

For the purposes of this symptom analysis we have used 40 of the best-documented cases in which there was involvement of at least two of the main branches, of which at least one was a common carotid artery. In 29 of the 40 cases all four main arteries were involved (clinically it is easiest to think of four large branches of the aortic arch although, of course, there are usually only three and sometimes only two).

The cerebral manifestations of the aortic arch syndrome differ in no respect from those of internal carotid thrombosis, which has been reviewed thoroughly elsewhere.[9] Vertigo, particularly on rising from the horizontal position, was the most frequent cerebral manifestation, occurring in at least 25 of the 40 cases. Loss of consciousness occurred in at least 15 cases. Hemiparesis or hemiplegia occurred in 13, convulsions in 8. In some instances headache was an exceedingly distressing symptom, as in Gull's patient,[10] whose headache "she said was such as almost to drive her mad." In those cases in which the aortic arch syndrome is part of a generalized arteritis, cephalic arteritis may be the cause of the headache. Patient

4. Edholm, O. G., Howarth, S., and Sharpey-Schafer, E. P.: Resting Blood Flow and Blood Pressure in Limbs with Arterial Obstruction, Clin. Sc. **10**:361, 1951.

5. Burchell, H. B.; Taylor, B. E.; Knutson, J. R. B., and Wakim, K. G.: Coarctation of the Aorta with Hypotension in the Left Arm: Physiologic Observations on Direct Intra-Arterial Pressures and Flow of Blood, M. Clin. North America **34**:1177, 1950.

6. Deneke, T.: Regarding Syphilitic Aortitis, Deutsche med. Wchnschr. **39**:441, 1913

7. Lewis, T., and Stokes, J.: A Curious Syndrome with Signs Suggesting Cervical Arterio-Venous Fistula: With Pulses of Neck and Arm Lost, Brit. Heart J. **4**:57, 1942

8. Gaertner, G.: Concerning a New Blood Pressure Measuring Device (Tonometer), Wien med. Wchnschr. **49**:1412, 1899.

9. (*a*) Amali, N. O., and Ashby, D. W.: Non-Traumatic Thrombosis of the Carotid Artery, Lancet **2**:1079, 1949. (*b*) Beck, W.: Thrombosis of the Carotid Artery, Thesis, University of Amsterdam, 1950. (*c*) Galdston, M.; Govons, S.; Wortis, S. B.; Steele, J. M., and Taylor, H. K.: Thrombosis of the Common, Internal and External Carotid Arteries: A Report of 2 Cases with a Review of the Literature, Arch. Int. Med. **67**:1162, 1941. (*d*) Hunt, R. J.: The Role of the Carotid Arteries in the Causation of Vascular Lesions of the Brain: With Remarks on Certain Special Features of the Symptomatology, Am. J. M. Sc. **147**:704, 1914. (*e*) Johnson, H. C., and Walker, A. E.: The Angiographic Diagnosis of Spontaneous Thrombosis of the Internal and Common Carotid Arteries, J. Neurosurg. **8**:631, 1951.

10. Gull, W.: Thickening and Dilation of the Arch of the Aorta with Occlusion of the Innominata and Left Carotid: Atrophic Softening of the Brain, Guy's Hosp. Rep. **16**:12, 1855

E. F. (p. 730) had pain first in one side of the neck, then the other, with occipital headache due probably to the arteritis itself. In the sitting position the patient sometimes [2a] finds it most comfortable to hang the head forward, which gives an impression of shyness. Impairment of memory was specifically commented on in four cases. Paresthesias of parts of the body were prominent in only four cases.

The changes in the eye are striking, probably because of the well-known sensitivity of the ocular structures to ischemia. Transient visual disturbances (amaurosis fugax) were reported by 17 patients. Some complained of dimness of vision when arising rapidly from a sitting position. Others noted "black spots" or "blinding light" before the eyes at times when the carotid blood flow was presumably reduced. Many complained of transient periods of complete blindness, often only on the side of the occluded carotid artery, with subsequent spread to the opposite eye. Three patients complained of dimness of vision associated with exercise. Visual acuity would be markedly reduced by walking or other exertion and would return with rest. Frøvig [3] referred to this symptom as "visual claudication." In 12 patients cataracts developed rapidly, often at an early age. Shimizu and Sano [2a] reported cataracts in 18 of 29 cases. Retinal atrophy and pigmentation were observed in six cases. Atrophy of the iris and leucomata or some corneal change were reported in seven cases. In their two cases Skipper and Flint describe the appearance of a new-formed circular vessel at the base of each iris.[11] Sluggish blood flow in the retinal vessels was demonstrated in seven patients, with easy obliteration of blood flow by light pressure on the eye-ball (a test for retinal arterial pressure). Aneurysmal nodulations were seen on the arterioles in three instances, and the progressive development of peripapillary arteriovenous anastomoses was frequently noted.[2b] One pair of authors, who published a beautiful color illustration of "wreath-like arterial anastomoses around the papillae," stated that these were observed in 24 of 29 cases.[2a] Two patients complained of photophobia, and optic atrophy was noted in several.

Changes in the auditory mechanism occurred but were not prominent manifestations. Deafness was described in three patients,[12] and tinnitus in at least one.[13] Numbness or pain in the scalp, presumably due to vascular insufficiency, was noted by three patients. Claudication in the jaw muscles was noted by one patient and continuous pain in the teeth by another. The trophic or nutritional changes seem to occur only in the head and neck. As a rule no changes in the hands or fingers of the type seen in thoracic outlet disease have been recorded. The trophic changes in the eye have already been discussed. Similar lesions develop elsewhere in the head and neck. Perforation of the nasal septum was seen at least three times,[14] while collapse of the bridge of the nose with saddle nose deformity was seen in at

11. Skipper, E., and Flint, F. J.: Symmetrical Arterial Occlusion of Upper Extremities, Head, and Neck: A Rare Syndrome, Brit. M. J. **2**:9, 1952.

12. (*a*) Black, D. M.: Absence of Pulse, Chinese M. J. **45**:552, 1931. (*b*) Crawford, J. R.: Bilateral Pulse Obliteration in Thoracic Aneurysm, J. A. M. A. **76**:1395, 1921. (*c*) Marinesco, G., and Kreindler, A.: Progressive and Complete Obliteration of the 2 Common Carotids with Epileptic Fits: Consideration of the Role of the Carotid Sinus in the Pathogenesis of Epileptic Fits, Presse méd. **44**:833, 1936.

13. Harbitz, F.: Bilateral Carotid Arteritis, Arch. Path. **1**:499, 1926.

14. Cacamise and Whitman.[2b] Marinesco and Kreindler.[12c] Harbitz.[13]

least one case.[15] The nasal perforation probably represents infarction of the cartilaginous septum. Trophic ulcer of the tip of the nose occurred once.[2b] Atrophy of one side of the face was seen in three cases. One writer [16] describes atrophy of the face muscles, with loss of wrinkling and facial expression and an appearance as though the skin rested directly on the craniofacial bones. Infections about the face healed poorly. Abnormal pigmentation of the face was observed in two cases and ulcer of the scalp in one. The hair may lose its luster and begin to fall out.[2a] The occurrence of these trophic changes in the distribution of the carotid arteries in the absence of similar changes in the arms suggests either greater susceptibility of the head structures or poorer collateral circulation. Both factors may play a role.

The cardiovascular manifestations are more difficult to evaluate, as many considered here are undoubtedly due to associated cardiovascular disease. Dyspnea was recorded in 11 cases. Angina pectoris occurred in four cases. Evidence of peripheral vascular insufficiency, as manifested by color, temperature, or skin changes in the arms, was seen in six cases. In most of the cases in which the arms were pulseless the circulation appeared to be perfectly adequate. Only two patients complained of claudication in the arms. A satisfactory collateral circulation undoubtedly developed concomitantly with the gradual occlusion of the larger arteries. This collateral circulation has been demonstrated after death in several of the patients [17] and clinically as dilated vessels over the back of the chest in four patients.[18] In some of these cases direction of flow was shown to be from below upward. Clubbing of the fingers, an occasional unilateral phenomenon in aneurysm, occurred bilaterally in a patient with aortic aneurysm and occlusion of all four branches.[12b]

A sensitive carotid sinus was demonstrated in seven of these cases.[19] Stimulation of the sinus precipitated syncopal attacks. This phenomenon was also recorded in the cases of Galdston [9c] and Smith.[20] In this connection, the case reported by Roseman and his associates [21] may be pertinent. In this patient a sensitive carotid sinus developed after ligation of the ipsilateral common and internal carotid arteries in treatment of intracranial arteriovenous aneurysm. The patient was relieved of

15. Aggeler, P. M.; Lucia, S. P., and Thompson, J. H.: A Syndrome Due to the Occlusion of All Arteries Arising From the Aortic Arch: Report of a Case Featured by Primary Thrombocytosis and Autohemagglutination, Am. Heart J. **22**:833, 1941.

16. Gadrat and Moreau: Thrombosis of the Branches of the Aortic Arch, Arch. mal. cœur **45**:830, 1952.

17. (*a*) Elliot, A. H.; Ussher, N. T., and Stone, C. S.: Bilateral Denervation in a Patient Having Syncopal Attacks and a Congenital Vascular Anomaly: Report of an Unusual Case. Am. Heart J. **17**:69, 1939. (*b*) Marinesco and Kreindler. [12c]

18. (*a*) Bittorf, A.: The Development of Arterial Collaterals After Obstruction of the Great Vessels of the Arms and Neck, Med. Klinik **42**:422, 1947. (*b*) Türk, W.: Arterial Collateral Circulation in Occlusion of the Great Vessels at the Aortic Arch by Deforming Aortitis, Wein klin. Wchnschr. **14**:757, 1901. (*c*) Skipper and Flint. [11]

19. (*a*) Richards, F. A.: Symmetrical Arterial Occlusion, Brit. Med. J. **2**:285, 1952. (*b*) Footnote 2. (*c*) Marinesco and Kreindler. [12c] (*d*) Gadrat and Moreau. [16] (*e*) Elliot, Ussher, and Stone. [17a] (*f*) The case of W. B., presented in this paper.

20. Smith, H. L., and Hinshaw, H. C.: Syncopal Attacks Due to a Congenital Anomaly of the Right Common Carotid Artery, Am. Heart J. **11**:619, 1936.

21. Roseman, E.; Whitcomb, B. B., and Woodson, F. G.: Carotid Sinus Syncope Secondary to Ligation of Carotid Vessels for Intracranial Arterio-Venous Aneurysm, J. Neurosurg **2**:287, 1945.

the carotid sinus symptoms by a second operation, in which the carotid bifurcation was completely removed. It is said [28a] that hyperpnea is a conspicuous feature of the response to carotid sinus pressure and may be the only type of response.

The blood pressure was recorded in the legs in 24 patients. In 15 of these the systolic pressure was greater than 160 mm. Hg. Authors writing before the introduction of clinical sphygmomanometry occasionally noted that the pulses in the legs were stronger than usual.[22] Frøvig [3] observed hypertension in the lower extremities and mentions it as one of the cardinal features of the "young female" arteritis variety (cf. p. 729) of the aortic arch syndrome (the term "reversed coarctation" applied to this set-up by others [23] serves no useful purpose, however). Central ischemia has been suspected as an etiological factor in hypertension since the early experiments in dogs by Starling.[24] The clinicopathologic studies of Bordley and Baker [25] were inconclusive. However, Fishback and co-workers [26] and Williams and Schroeder [27] have produced chronic hypertension in the dog by progressive ligation of the arteries supplying the head.

Systolic bruits over partially occluded branches of the aortic arch have been frequently encountered. In at least five patients continuous murmurs resembling that of arteriovenous fistula were present. All five were young white women with no evidence of syphilis or other definite cause of the disorder. In two patients [28] the continuous murmur was at the base of the neck on the right just above the sternoclavicular joint; in three others it was located in a comparable position on the left [29] and was at times thought to indicate a patent ductus arteriosus. Against this interpretation was the atypically high location of the murmur under discussion. Sato [30] and Oota [31] refer to cases of the aortic arch syndrome in which the diagnosis of patent ductus arteriosus (botalli) was made, presumably on the basis of a continuous murmur. In the light of these other cases an obvious alternative possibility exists. The only plausible explanation for the machinery murmur in these cases

22. Parsons, C.: Case of Occlusion of the Arteries Arising from the Arch of the Aorta: With Aortic Degeneration and Aneurisms, Boston M. & Surg. J. **86**:400, 1872.

23. (a) Giffin, H. M.; Dry, T. J., and Horton, B. T.: Reversed Coarctation and Vasomotor Gradient: Report of a Cardiovascular Anomaly with Symptoms of Brain Tumor, Proc. Staff Meet. Mayo Clin. **14**:561, 1939. (*b*) Lampen, H., and Wadulla, H.: Stenosing Syphilis of the Aorta with the Clinical Picture of "Reversed Coarctation," Deutsche med. Wchnschr. **75**:144, 1950.

24. Starling, E. H.: The Physiological Factors in Hyperpiesia, Brit. M. J. **2**:1163, 1925.

25. Bordley, J., III, and Baker, B. M., Jr.: Arteriosclerosis of the Cerebral Vessels and the Pathogenesis of Hypertension, Bull. Johns Hopkins Hosp. **39**:229, 1926.

26. Fishback, H. R.; Dutra, F. R., and MacCamy, E. T.: The Production of Chronic Hypertension in the Dog by Progressive Ligation of the Arteries Supplying the Head, J. Lab. & Clin. Med. **28**:1187, 1943.

27. Williams, A. H., and Schroeder, H. A.: Regional Vasomotor Tone in Normotensive and Hypertensive Dogs, Circulation **4**:706, 1951.

28. Lewis and Stokes.[7] Giffin, Dry, and Horton.[23a]

29. (*a*) Southworth, J. L.; McKusick, V. A.; Peirce, E. C., II, and Rawson, F. L., Jr.: Ventricular Fibrillation Precipitated by Cardiac Catheterization: Complete Recovery of the Patient After 45 Minutes, J. A. M. A. **143**:717, 1950. (*b*) Skipper and Flint.[11] (*c*) Aggeler, Lucia, and Thompson.[15]

30. Sato, T.: An Unusual Case of Arterial Obliteration, Klin. Wchnschr. **17**:1154, 1938.

31. Oota, K.: Rare Case of Bilateral Carotid-Subclavian Occlusion: Contributions to Pathology of Peripapillary Anastomosis of the Eye with Absence of Radial Pulse, Soc. path. jap. **30**:680, 1940.

would appear to be that it is produced by the flow of blood through dilated and tortuous arterial collaterals. A bruit which was heard over the dilated arterial collaterals over the back of the thorax has also been described.[32]

In the sections that follow it is proposed to discuss some of the etiologic types of the aortic arch syndrome. The cases reported in abstract form in these discussions will serve to illustrate the several features that constitute this syndrome.

ETIOLOGIC TYPES OF THE AORTIC ARCH SYNDROME

Cases of Obscure Nature.—Our attention was attracted to the aortic arch syndromes by the following case of obliterated pulses of obscure origin.

W. W. (J. H. H. 587768), a 45-year-old white man, was admitted on Oct. 16, 1951, because of visual, cerebral, and arm symptoms.

There was no history of syphilis, and serological tests had always been negative. In 1937, fourteen years before the first admission to this hospital, the patient was involved in an automobile accident. He was thrown against the steering wheel, fracturing several ribs and depressing the upper sternum. Recovery was satisfactory without restorative surgery, and there were no chest symptoms after initial recovery.

In May 1950, eighteen months before this admission, the patient was seen by his local physician because of irregular heart action and was found to have ventricular premature contractions and a blood pressure of 122/80 mm. Hg.

During September 1950, thirteen months before admission, the patient first complained of black spots before his right eye for brief periods, occasional episodes of diplopia, and transitory feelings of dizziness relieved by lowering the head. In November 1950 the first attack of transient complete blindness in the right eye occurred. Physical examination during this period showed spasm of the retinal arterioles and blood pressure of 140/80 mm. Hg in the left arm and 130/80 mm. Hg in the right. During January 1951 the patient noted aching in the right arm when shaving, combing his hair, or polishing the roof of his car. Examination at this time showed a blood pressure of 130/80 mm. Hg on the left as opposed to 90/70 mm. Hg on the right. The right radial and right carotid pulses were absent at this time. X-ray and fluoroscopic examination at another hospital revealed no abnormality of the heart, mediastinum, or great vessels. The proximal portions of the right subclavian and right carotid arteries were visualized by angiocardiography and were believed to be normal. In July 1951 the patient first experienced aching in the left arm similar to that observed in the right seven months previously. The left radial pulse was absent, and no blood pressure reading was obtained in either arm. There was no history of unconsciousness or convulsions, but the patient recalled several brief periods of spatial disorientation in familiar surroundings. He did not complain of dyspnea, chest pain, or ankle edema, and there were no symptoms of acute arterial occlusion.

Positive physical findings (in October 1951) were limited to the cardiovascular system. The blood pressure was 195/100 mm. Hg in the legs and was unobtainable in the arms. Oscillations of the manometer were seen as the pressure in the cuff was reduced between 100 and 60 mm. Hg. A short faint bruit was heard in the antecubital fossae with tensions of 60 to 80 mm. Hg. The right radial, brachial, carotid, temporal, and external maxillary pulsations were absent. The left brachial and radial pulsations were likwise absent. Good pulsation was noted in the left carotid and its branches as well as in the vessels in the lower extremities. The arms were normal and equal with regard to temperature, color, and skin texture. The heart was not enlarged, the rhythm was regular, and the sounds were of normal quality. A Grade I systolic murmur was heard in the third and fourth left interspaces at the sternal border. The lungs were normal. There was a slight depression of the sternum below the angle of Louis, but no marked angulation or excavation. Small subcutaneous lipomata were noted on the arms. The remainder of the physical examination was not remarkable. The patient was in excellent general health.

32. Skipper and Flint.[11] Gadrat and Moreau.[16]

Laboratory examinations revealed a negative serological test for syphilis; a negative treponemal immobilization test (Nelson[33]); hemoglobin 16.0 gm. per 100 cc.; hematocrit level 47%; sedimentation rate 8 mm. per hour; white cell count 9,000 per cubic millimeter, with polymorphonuclear cells 57%, eosinophiles 11%, lymphocytes 29%, and monocytes 3%; platelets 234,000 per cubic millimeter; serum cholesterol 355 mg. per 100 cc. Stool was negative for occult blood but contained cysts of Endamoeba histolytica. The urine was normal in all respects.

Fluoroscopy failed to demonstrate any abnormality in the chest. There was no cervical rib. The angiocardiograms taken in February 1951 were reviewed, and no further interpretation could be made. Venous pressure, phenolsulfonphthalein-excretion test, and circulation time with dehydrocholic acid, N. F. (Decholin) were normal. Electrocardiogram showed a PR interval of 0.20 seconds and a QT interval at the upper limits of normal. Electroencephalogram was within the normal limits. A subcutaneous nodule was excised from the arm along with underlying muscle. The nodule was a lipoma, and the muscle was normal. The ophthalmological consultant noted minimal retinal arteriosclerosis and corneal changes consistent with the history of a gunpowder burn in childhood.

In this case of obstruction of great vessels developing over the course of one year no definite etiology could be established. It was suggested that the chest trauma might have predisposed to premature degenerative changes in the aortic wall, possibly atheromatosis, with subsequent thrombosis. There is pathological evidence that damage to the intima of the great vessels may occur with injuries of the type this man sustained (see below, Traumatism). Experimental damage to the elastica of arteries, as by mechanical rupture from stretching, results in a proclivity to the development of intimal atheromatosis in cholesterol-fed rabbits.[34] That premature atheromatosis might have occurred at the sites of damage in the above patient is conceivable. Localization of changes to the ostia of the great vessels may be a function of the shearing injury from depression of the sternum. The 13-year interval between the traumatic episode and the first symptom makes an association problematical yet conceivable.

A second case of aortic arch syndrome of obscure origin has come to our attention.

E. L. (J. H. H. 505915), a 33-year-old Indian woman from Trinidad, entered the service of Dr. Warde Allan, complaining of severe substernal pressure and pain radiating to the left side of her neck and into her left arm during the five years prior to admission. The patient noted that this pain was definitely related to exertion and was relieved by rest. There were no other cardiovascular symptoms. Physical examination was not remarkable except as it concerned the cardiovascular system. The blood pressure in the left arm was 65/45, in the right arm 60/40, and in the right leg 100/75 mm. Hg. The left carotid artery was palpable, strongly pulsating with systolic thrill and murmur. The right carotid pulse was normal. The heart was enlarged to the anterior axillary line in the fifth interspace. There were systolic and diastolic murmurs heard in the second right interspace and transmitted along the right sternal margin. Results of routine blood, urine, and chemical examinations were normal. Serological tests for syphilis and spinal fluid Wassermann reaction were negative. Electrocardiogram showed only left ventricular strain. Fluoroscopy of the chest showed an enlarged left ventricle, with extensive calcification of the aorta extending from the arch to a point well below the diaphragm.

The patient was explored by Dr. Alfred Blalock, on July 11, 1949, who found the aorta to be a "rigid calcified tube" from the midportion of the arch to the diaphragm. There was absolutely no expansile pulsation in this part of the aorta. The first part of the left subclavian artery for a distance of 3 or 4 cm. was a calcified tube. No calcified coronary vessels were palpated

33. Nelson, R. A., and Mayer, M. M.: Immobilization of Treponema Pallidum in Vitro by Antibody Produced in Syphilitic Infection, J. Exper. Med. **89**:369, 1949.

34. Ssolowjew, A.: Experimentally Produced Tearing of the Elastica of Arteries and Its Significance in Lipoid Deposition, Arch. path. Anat. **283**:213, 1932.

through the pericardium. Samples of skeletal muscle and the internal mammary artery were taken and found to be normal histologically. A left dorsal sympathectomy was performed. The patient was discharged with the diagnosis of idiopathic calcification of the aorta.

The patient died a few months after returning to Trinidad. Unfortunately no postmortem examination was performed.

The etiology in this case is obscure. It may represent calcification of cystic medial necrosis or some other type of medial degeneration. Obviously syphilis is not excluded, nor is well-healed dissecting aneurysm.

In the literature there are, as might be expected, several reports of cases in which the etiology is obscure. Such a case is that reported by Savory [35] in 1856. The patient was a 22-year-old woman who was admitted to St. Bartholomew's in 1854 with severe pain of the left side of the head, giddiness, disturbances of vision, dyspnea, and "a sense of constriction and uneasiness in the left region of the chest, with occasional palpitation." No pulses had been palpable in the arms for at least five years; the absence of pulses had been observed on admission to Guy's Hospital in 1853. She suffered about that time with localized fits of the right arm and leg. These extremities became progressively weaker. The examination revealed complete absence of pulses in both arms and in the left carotid artery, feeble pulsation in the right carotid artery, a loud harsh systolic bruit over the manubrium sterni, and a soft bruit in the course of the right common carotid. Vision was impaired in both eyes but was better when the patient was lying down. Later she complained of complete loss of vision on standing. The patient was in the hospital 13 months before she died. There was progressive debilitation. A large gangrenous slough occurred in the left parietal region, with exposure of the left cerebral hemisphere. The right-sided fits continued; complete loss of vision in the left eye occurred. At autopsy the heart, its muscular tissue, its investing and lining membranes, and the cardiac and arterial valves, were found to be healthy. The aorta at its commencement presented no appearance of disease. However, beginning at the proximal end of the aortic arch and extending throughout the descending thoracic aorta "the lining membrane was uniformly dull and opaque. The coat itself separated from the middle tunic with morbid facility." In all branches of the aortic arch the "internal coat separated with the slightest force from the middle" and "irregular patches of an opaque yellowish deposit, in considerable quantity, were found between the two." The vessels became fibrous a few inches beyond their origin from the aorta. The pathological description suggests healed dissecting aneurysm of the aorta.

There are several other cases in the literature [36] which were too inadequately described or from which insufficient data were obtainable to permit an etiologic diagnosis. Brown's case [36b] is interesting in that it was possible to date the onset of the pulse abnormality quite exactly, as a result of observations by native Chinese physicians. The long-standing Oriental interest in the pulse is reflected by the rela-

35. Savory, W. S.: Case of a Young Woman in Whom the Main Arteries of Both Upper Extremities, and of the Left Side of the Neck Were Throughout Completely Obliterated, Med.-Chir. Tr. **39**:205, 1856.

36. (*a*) Baumler: München. med. Wchnschr. **54**:2500, 1907. (*b*) Brown, C. F.: Absence of Pulse: A Case of Absence of Pulse in Both Axillary, Radial, and Carotid Arteries, While Normal in the Femorals and Dorsalis Pedis Arteries, Chinese M. J. **43**:269, 1929. (*c*) DeMeyer, J.: Cerebral Anemia from Carotid Maldevelopment, Arch. mal. cœur **14**:11, 1921 (*d*) Smith and Hinshaw. [20]

tively large number of Chinese and Japanese publications on the subject under discussion here.[37] Caccamise and Whitman [2b] found 58 cases of this syndrome reported from Japan. This may indicate a higher incidence of one of the etiologic varieties of this syndrome, probably idiopathic arteritis.

Syphilitic Aortitis with Aneurysm.—Generally the presence of inequality of radial pulses first suggests to the clinician the presence of aortic aneurysm. In 1628 in *De Motu Cordis,*[38] Harvey described a case in which "the pulse in the corresponding arm was small in consequence of the greater portion of the blood being diverted into the tumor and so intercepted." William Hunter [39] described in 1757 a case in which the pulse was absent in the left arm and temple following the development of an aortic aneurysm. E. Marey [40] in 1881 for the first time recorded pulsus differens in a case of aortic aneurysm by means of his sphygmograph. Actually pulse abnormalities due to aortic aneurysm are much less frequent than is commonly thought. An analysis by Hare and Holder [41] in 1899 revealed that in only 32 cases out of 953 were pulse abnormalities noted. Of the 272 cases in which specific description of the pulses was made, 32, or 12.2%, were abnormal, while in only 5, or 1.9%, was total absence of pulsation noted. If it is assumed that the pulses were normal when not described, the percentages, of course, become much smaller.

Boyd,[42] in reviewing 4,000 cases of aneurysm of the thoracic aorta, in 1924, describes inequality of the two pulses and delay of one pulse but makes no mention of complete obliteration. In a group of 100 recent cases of thoracic aneurysm at the Johns Hopkins Hospital in only 1 case was pulse abnormality described. However, at least four other patients with aortic arch syndrome due to syphilitic aortic aneurysm are known to the authors.

Complete obliteration of pulses in both upper extremities and in the neck has been reported in aortic aneurysm in a total of at least seven cases. The first such case was apparently one of John Davy's,[43] reported in 1839. The patient was

an officer of rank, aged about 55, distinguished for his services in the field during the Peninsular War, and who had been severely wounded in the chest at Waterloo. During the winter of 1834-5 he was in a valetudinary state. In August of 1835 he was seen by Dr. Chambers who mentioned

37. (*a*) Oda, M.: Studies of Pulsus Differens in the Upper Extremity, Acta scholae med. univ. Kioto **12**:469, 1930. (*b*) Takahasi, K.: Percutaneous Arteriography of the Vertebral Arteries and Their Branches, Arch. Psychiat. **111**:373, 1940. (*c*) Yoshino, G.: Pulsus Differens and the Maximum Blood Pressure Difference in Both Arms, Acta scholae med. univ. Kioto **16**:317, 1933-1944. (*d*) Shimizu and Sano.[2a] (*e*) Black.[12a] (*f*) Sato.[30] (*g*) Oota.[31] (*h*) Brown.[36b]

38. Harvey, W.: Anatomical Studies on the Motion of the Heart and Blood, Leake Translation, Springfield, Ill., Charles C Thomas, Publisher, 1931.

39. Hunter, W.: The History of an Aneurism of the Aorta with Some Remarks on Aneurisms in General, in Medical Observations and Inquiries, London, 1757, Vol. 1, pp. 323-357

40. Marey, E.: The Circulation of the Blood, Paris, Masson & Cie., 1881.

41. Hare, H. A., and Holder, C. H.: Some Facts in Regard to Aneurysm of the Aorta, Am. J. M. Sc. **118**:399, 1899.

42. Boyd, L. J.: A Study of 4,000 Reported Cases of Aneurysm of the Thoracic Aorta, Am. J. M. Sc. **168**:654, 1924.

43. Davy, J.: Notice of a Case in Which the Arteria Innominata and the Left Subclavian and Carotid Arteries Were Closed Without Loss of Life, in Researches, Physiological and Anatomical, London, Smith, Elder & Co., 1839, Vol. 1, p. 426.

that he 'never could perceive any pulse from the time he first saw him.' In September he was taken suddenly and seriously ill with tendency to syncope and vertigo frequently recurring, then it was certain that no pulse could be perceived at either wrist. His disease now was clearly aneurism of the arch of the aorta, with an obstructed state (it might be inferred) of the great vessels arising from it; for *no pulse could be felt anywhere in the course of these vessels, neither the neck, temples, axilla, or wrists,* and there was a throbbing pulse at the upper part of the sternum, and a slight prominence of the bone there to some little extent. On the 11th of January, 1837, that is, nearly a year and a half from the cessation of the pulse at the wrist, he expired suddenly. A *post mortem* examination was made by a very competent surgeon. The pericardium was found distended with coagulated blood, and a small fissure was detected in the aorta near its base, through which the blood had penetrated. The heart was rather large, and its cavities large, but without distinct hypertrophy; its valves natural. The arch of the aorta was, as had been inferred, the seat of a large aneurism, about six inches high, and about four inches wide, nearly filled with coagulum, dense, fibrous, and nearly white, occupying all but the inferior space, where there was a channel open by which the blood passed from the heart into the descending portion of the vessel. Where the vessel commenced its descent, there were some atheromatous deposits on it, and a few bony scales. All the great vessels rising from the arch were completely closed, as far as they were examined, namely to the extent of about two inches, were impervious, plugged up with lymph.

In this case it appears quite certain that the aneurysm was syphilitic. A role of the severe chest wounds sustained at Waterloo is doubtful.

A well studied and colorfully described early case is that of Parsons.[22] The patient, an American Civil War Veteran, aged 39, had obliteration of all four main branches of the aortic arch due to aneurysm. He was seen by Dr. Austin Flint. Necropsy revealed that both thrombus plugs and cicatricial stenosis were operative in the occlusive disease. This patient had sustained a severe chest wound during the war, four years before the onset of symptoms.

Without specific details, Osler[44] wrote in 1908 that "there are cases in which no pulsation is felt in any of the arteries of the head or of the upper extremities, generally instances of large aneurism of the transverse arch."

Shikhare[45] in 1921 reported the following case: A middle aged carpenter was examined because of frequent attacks of giddiness, and absence of pulsation was noted over all the arteries of the upper half of the body: the temporals, the carotids, the brachials, and the radials. The pulsations of the abdominal aorta and arteries of the lower extremities were normal. At postmortem examination

the ascending aorta and the arch showed a fusiform aneurysmal dilatation, which was occupied by a large ante-mortem clot obliterating almost the whole of its lumen. This large central clot sent diverticula extending into and almost obliterating the lumen of the innominate artery with its branches, the right common carotid and the right subclavian and also into the corresponding arteries of the left side to a variable extent. These diverticula acted as loosely fitting plugs for the different arteries mentioned, thus allowing a certain amount of blood to pass beyond but cutting off a greater part of the current.

Other cases of bilateral absence of pulses in the head and arms with syphilitic aortic aneurysms were reported by Crawford,[12b] Kampmeier, and Neumann,[46] Cohen

44. Osler, W.: Modern Medicine, Philadelphia, Lea & Febiger, 1908, Vol. 4, p. 476.

45. Shikhare, P. V.: Notes on a Remarkable Case of Absence of Pulsation in the Arteries of the Upper Parts of the Body, Indian J. Med. **2**:326, 1921.

46. Kampmeier, R. H., and Neumann, V. F.: Bilateral Absence of Pulse in the Arms and Neck in Aortic Aneurysm, Arch. Int. Med. **45**:513, 1930.

and Davie,[47] and Maurer (second case).[48] Postmortem confirmation was not available in the cases of Crawford and Kampmeir and Neumann, but the clinical diagnosis of aneurysm was well established. Darling [49] (Case IV) describes a case of aortic aneurysm in which " the orifices of the branches were all partly occluded by proliferated intima, but that of the left subclavian was completely obliterated." The pulses during life were not described.

With regard to occlusion of the vessels coming from the arch, Cohen and Davie [47] point out that the pathological findings are of two types. In some instances projecting fingers of antemortem thrombus were described as occluding various branches of the arch. Davy's case [43] and Shikhare's case,[45] cited above in detail, are examples. In Maurer's second case,[48] "glove-finger projections of the antemortem thrombus situated in the aneurysm extended into and completely occluded the innominate, left common carotid, and left subclavian arteries." In other cases it is clear that the obliteration is cicatricial in mechanism. In these cases it is usually stated that the ostia are indicated only by dimples in the wall of the aneurysm—"indented cicatrices" (Gull,[10] see illustration). Sometimes no indication of the location of the ostia can be found on the intimal surface. This is the same mechanism as that operative in cases of obliteration due to syphilitic aortitis without aneurysm. A typical case illustrating this mechanism is that of Cohen and Davie.[47] The patient had syncope, headaches, and blindness in the left eye; both radial and both carotid pulses were absent; the serological test for syphilis was positive, and the diagnosis of aneurysm was established by fluoroscopy. At necropsy

> the orifices of the three large vessels arising from the aortic arch were completely obliterated, their sites being represented merely by two shallow depressions. The depression marking the orifice of the innominate artery was somewhat deeper than that over the combined orifices of the left common carotid and left subclavian arteries. In each case, within the depression was a small irregular pit, which admitted a stout bristle for 1 to 2 mm. These pits seemed to be the last remnants of the arterial orifices.

In some cases both mechanisms are involved. Another example is Maurer's first case.[48]

Two other explanations for pulse differences in aneurysm are as follows: One, that advanced by Harvey,[38] is that the large saccular aneurysm distends with systolic ejection, absorbing the pulse wave and producing a more nearly continuous flow. The significance of this factor has been evaluated experimentally by Marey [40] and more recently by Whittlesey.[50] This is probably a contributing factor in some cases. The second possibility is that the vessels are obliterated by external pressure from the large aneurysmal sacs. This mechanism is well described in Suckling's case.[51] Certainly these mechanisms, while they could undoubtedly account for pulse differences, would not usually produce complete obliteration of the pulse.

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47. Cohen, H., and Davie, T. B.: Bilateral Obliteration of Carotid and Radial Pulses by Aortic Aneurysm, Lancet **1**:852, 1933.

48. Maurer, E.: Absence of Pulse in the Vessels of the Upper Extremities and Neck in Aneurysm of the Aortic Arch. Am. Heart J. **17**:716, 1939.

49. Darling, S. T., and Clark, H. C.: Arteritis Syphilitica Obliterans: A Pathological Report of Several Cases of Complete Occlusion of Large Arteries, Aorta, Carotid, and Subclavian, in Which Syphilis Was the Causative Factor, J. M. Research **32**:1, 1915.

50. Whittlesey, R. H.: Dynamic Changes in Arterial Pressure Pulses Produced by a Simulated Saccular Aneurysm, Am. J. Physiol. **168**:192, 1952.

51. Suckling, R.: A Case of Innominate Aneurysm: Death After Inhalation of Chloroform. Lancet **2**:245, 1885.

Kampmeier and Neumann [46] point out that congenital malformations of the aortic arch increase the chance of bilateral pulselessness occurring as a result of aneurysm. This is especially true if, as in the case of Cohen and Davie,[47] the malformation is such that the great vessels arise from two rather than three ostia.

Occlusion of one or more but not all vessels from the aortic arch by syphilitic aortitis with aneurysm has been reported by Gull,[10] Töppich,[52] Türk,[18b] Fraenkel,[53] Blakiston,[54] Pilz,[55] Erb,[56] Cooley,[57] Blake,[58] Suckling,[51] and Preisendörfer.[59]

Syphilitic Aortitis Without Aneurysm.—In this category we have considered cases in which the obliteration of pulses occurred with syphilitic aortitis without clinical and/or pathological evidence of saccular aneurysm. It is noted that complete obliteration of all four pulses in the upper part of the body occurs in this condition perhaps more frequently than in the group of patients with aneurysm. In several of the cases, however, there was diffuse dilatation of the aorta. The occlusions appear to be of the cicatricial type referred to above. Deneke [6] was one of the first to point out that aneurysm is not a *sine qua non* for the development of pulse abnormalities in syphilitic aortitis. He referred to 36 cases of pulse difference, in 7 of which no aneurysm was present. Aubertin [60] again emphasized pulsus differens as a sign of simple syphilitic aortitis.

The following seven cases from our own series are considered representative and most instructive. Postmortem examination was performed in the three which will be described first.

Case 1.—J. F. (J. H. H. 167130), a 45-year-old Negro, had a history of syphilitic infection with late antisyphilitic therapy. He died during appendectomy, presumably as a result of deep nitrous oxide anesthesia. At autopsy the aorta revealed typical intimal changes of syphilis, with moderate dilatation. The orifice of the left subclavian artery was "practically completely occluded." The right coronary ostium was also markedly narrowed by the syphilitic process.

Case 2.—S. P. (J. H. H. 35082), a 41-year-old Negro, had a history of untreated syphilis. When first seen, in 1931, the blood pressure was 124/85 mm. Hg in the right arm and 145/85 mm. Hg in the legs. Blood pressure was unobtainable in the left arm, and pulsations in the left carotid were variously described as faint or absent. A year later the blood pressure was recorded at 114/85 in the right arm and 85/75 in the left. The left carotid pulse was absent. The patient

52. Töppich, G.: Non-Thrombotic Occlusion of the Great Vessel Ostia at the Aortic Arch Especially the Ostium of the Left Common Carotid, Frankfurt. Ztschr. Path. **25**:236, 1921.

53. Fraenkel, E.: Two Cases of Aneurysm of the Aortic Arch Complicated by Total Occlusion of the Left Carotid, Virchows Arch. path. Anat. **79**:509, 1880.

54. Blakiston, P.: Clinical Observations on Diseases of the Heart and Thoracic Aorta. London, Longmans, Green & Co., Ltd., 1865, p. 169.

55. Pilz, C.: Regarding Ligation of the Common Carotid Artery, Arch. klin. Chir. **9**:259. 1868.

56. Erb, W., Jr.: A Case of Extensive Cerebral Softening Due to Total Obliteration of the Left Common Carotid, München. med. Wchnschr. **51**:946, 1904.

57. Cooley, L. E., and McNamara, F. P.: Syphilitic Aortitis with Aneurysm of the Innominate Artery and Occlusion of the Left Common Carotid Artery, Am. Heart J. **9**:686, 1934.

58. Blake, J. C.: Aneurism of the Innominate, Boston M. & Surg. J. **106**:418, 1882.

59. Preisendörfer, P.: A Case of Complete Obliteration of the Arteria Anomyna, Almost Complete of the Carotid and Left Subclavian, Complicated by Aneurysm of the Aorta and Carcinoma of the Esophagus, Arch. path. anat. **73**:594, 1878.

60. Aubertin, C.: The Diseases of the Aorta. Paris, A. Chahine, 1928, p. 38.

died suddenly soon after these observations. At autopsy the orifice of the left subclavian artery was completely occluded by gray fibrous tissue. The opening of the left carotid artery would "just admit a probe." The aorta was somewhat dilated, with syphilitic changes.

CASE 3.—S. W. (J. H. H. 466462), a 63-year-old Negro woman, was admitted to the hospital because of angina and heart failure. There was serologic evidence of syphilis, for which no treatment had been given. Blood pressure and pulse were unobtainable in the left arm. The patient died following acute posterior myocardial infarction. At autopsy the aorta was somewhat dilated, with "tree bark" wrinkling of the intima. The left subclavian artery was completely filled at its ostium by recanalizing thrombus. Openings of intercostal arteries were for the most part occluded, as was the ostium of the right coronary artery.

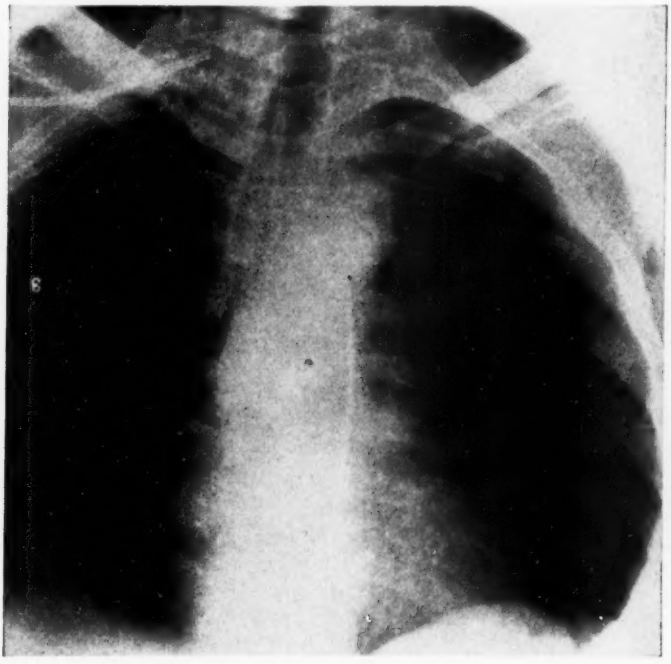

Fig. 1.—Retrograde aortogram of Patient A. L. The radio-opaque material was injected through a polyethylene catheter which was introduced percutaneously into the femoral artery and thence into the aortic arch. There was good evidence that syphilitic aortitis was the cause of the aortic arch syndrome in this patient.

CASE 4.—H. McG. (J. H. H. 152817), a Negro woman born in 1911, gave a history of inadequate antisyphilitic therapy. When she was first seen, in 1938, no pulses were palpable in either arm or in the neck. There was a localized systolic blow over the lower part of the right carotid artery. X-ray of the chest revealed slight to moderate dilatation and tortuosity of the aorta, with no evidence of saccular aneurysm. The pulse abnormality remained unchanged up to the time the patient was last seen, in 1942.

CASE 5.—E. M. (J. H. H. 585107), a white housewife born in 1893, was first admitted in 1932 because of angina. She was found to have serological evidence of syphilis. Examination revealed no pulses in either arm; a loud rough systolic murmer and thrill over the carotid arteries, which showed reduced pulsations, and a rather ringing second aortic sound. Blood pressure of about 80/76 mm. Hg was recorded from the left arm. X-ray showed moderate diffuse

dilatation of the aorta. The patient was first given potassium iodide by mouth, then bismuth subsalicylate intramuscularly, and finally neoarsphenamine intravenously. After therapy a remarkable clearing of angina occurred. The patient was not seen again until September 1951. Prognostic prediction had been entirely incorrect. She had done most of her housework herself and often went a month between attacks of angina, which were now mild. The radial pulses were now palpable and equal. The blood pressure was 140/92 mm. Hg in the right arm, 130/88 in the left. There appeared to be localized aneurysms in the upper right and lower left common carotid arteries, with overlying systolic thrills and bruits. X-ray of the chest showed slight diffuse dilatation of the aorta, with heavy calcification of the ascending portion.

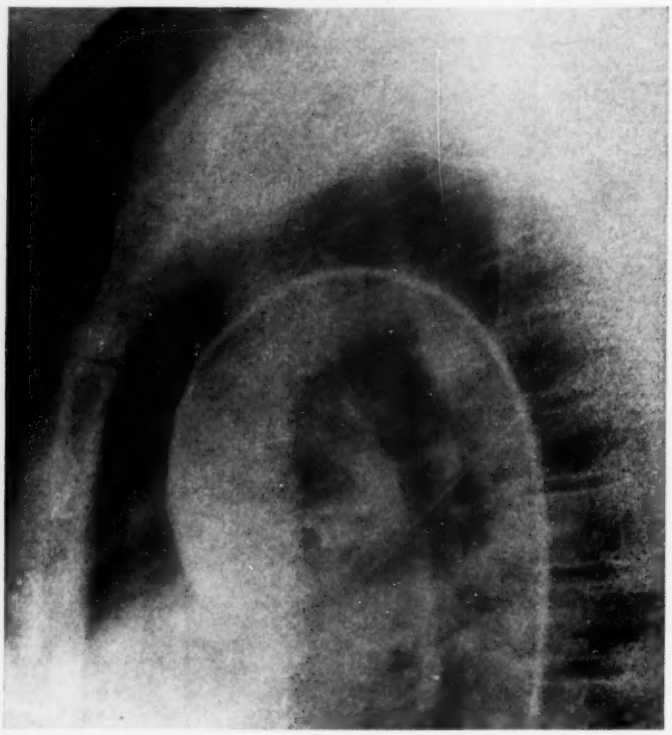

Fig. 2.—Retrograde aortogram of Patient A. L. Although not definitely identifiable in the anteroposterior projection (Fig. 1), a small saccular aneurysm at the arch is visible in the lateral view.

Case 6.—A. L. (J. H. H. 492165, Sinai 61685), a white man born in 1896, was admitted in 1949 because of convulsions and "low blood pressure" during the previous four years. There had been a total of about 14 generalized convulsions, many of which were precipitated by coughing paroxysms. A positive serological test for syphilis had been discovered in 1945, and therapy was given. Examination revealed no pulsations in any of the arteries of the arms and neck. Blood pressure was unobtainable in the arms and was 194/74 in the legs. Retrograde aortograms performed (by Dr. Henry T. Bahnson) by means of a catheter introduced via the right femoral artery revealed normal aortic caliber, with a small but definite saccular aneurysm at the arch (Figs. 1 and 2). An operative procedure performed on Sept. 20, 1950, by Dr. Gordan Murray of Toronto, is discussed in the section on therapy.

CASE 7.—W. B. (J. H. H. 514561), a 46-year-old white man, was admitted in 1949 for investigation of syncopal attacks and visual symptoms. In 1942 bilateral pulselessness of the arms, with unobtainable blood pressure, had been first noted by his physician. He was asymptomatic, however, until 1946, when he fell 25 ft, striking the left side of his body. He was intermittently unconscious for 12 hours and sustained fractures of three left lower ribs. Vision was absent in the right eye for four days and in the left eye for seven days. During the next three months there were several episodes of blindness in the left eye, lasting two to seven hours. These attacks were sometimes precipitated by movement, especially dorsiflexion, of the head. Attacks later appeared characterized by a "blinding yellow haze" spreading first over the right, then over the left field of vision; these were relieved by lowering the head between the knees. During the eight months before admission there occurred a total of six syncopal attacks, often precipitated by changes in position of the head and sometimes associated with involuntary twitching of the right arm. Angiocardiograms made at another hospital failed to show any filling of the subclavian or carotid arteries. Examination revealed absent brachial and carotid pulses bilaterally, although the vessels were readily palpable. The face paled perceptibly when the patient assumed an upright position. The retinal arteries showed peculiar knob-like protrusions resembling aneurysms. Carotid sinus pressure precipitated an attack of blanching, aphasia, and confusion, followed by jerking of the right arm and syncope. Serological tests for syphilis, including the treponemal immobilization test, were positive. Antisyphilitic therapy was given. A letter in November 1951 revealed that the patient was considerably improved and was working as a carpenter, with easy fatigability and paresthesias of the arms as the only complaints.

We have studied three other cases of occlusion of the carotid or innominate arteries due to syphilitic aortitis (R. G., 296195; A. S., 373986; A. L. S., 154454 B. C. H.). Only the more unusual and instructive cases have been described here.

Yelloly's case [61] of "preternatural growth in the lining membrane" of the aortic arch and the great vessels, reported in 1823, probably represents a case of syphilitic aortitis with superimposed arteriosclerosis. This man of 56 dropped dead while at work in a garden. His general health had always been good except for two or three attacks of sudden faintness during the two years before death. The state of the pulse was not known. At postmortem examination

> the whole of the ascending aorta was somewhat increased in diameter, and its inner surface, in many places, covered with irregular scales of ossification. The trunk of the arteria innominata was reduced to less than one-third of its usual dimension. In the left carotid the opening of the trunk into the aorta was diminished to such an extent, as to admit not more than the passage of a common-sized probe.

The left subclavian orifice was diminished "to the extent of a small slit."

Cases almost certainly of multiple vessel occlusion by simple syphilitic aortitis were graphically described by Yelloly [61] in 1823 and Davy [43] in 1839 (patient Hector McCallum). Regarding pathogenesis, Davy made the following observation:

> I am disposed to believe that whenever the middle coat of an artery becomes diseased, whether from atrophy, or change of structure, or deposition in it, of that matter which has been called atheromatous, or any other, there is invariably an effort, as it were, made, to strengthen the part, by the deposition of lymph on both sides; and that according to the rate of progress of the two processes, there is either a closure of the vessel, or an aneurism established: if the lymph is deposited rapidly, the former, if the atheromatous matter the latter; and also the latter, if the absorption or weakening of the middle coat from diseased alteration in its texture proceed with more speed than the deposition of lymph.

61. Yelloly, J.: Case of Preternatural Growth in the Lining Membrane Covering the Trunks of the Vessels Proceeding from the Arch of the Aorta, Med.-Clin. Tr. **12**:565, 1823.

This theory agrees remarkably well with current views on the pathogenesis of syphilitic aortitis and offers an adequate explanation for the production of either aneurysm or occlusion by the same disease process.

One of our patients with syphilitic aneurysm of the aorta (J. H. H. 373986) had a Corrigan pulse in the right arm, with a blood pressure of 180/20 mm. Hg, while the pressure in the left arm was 120/82 mm. Hg, with no Corrigan pulse. Motley and Moore [62] reported a similar case, in which a Corrigan pulse was corrected in one arm by syphilitic stenosis of the subclavian orifice.

Cases in this category have also been described by Snow,[63] Thompson,[64] Darling and Clark (Cases II, III, and VI),[49] Barker,[65] Sato,[30] Riegel,[66] Cooley,[57] Black,[12a] Pijoan de Beristain,[67] Casiello and Hanono,[68] Lampen and Wadulla,[23b] and Richards.[19a] Barker's case was extremely well documented and demonstrated postmortem changes of syphilitic aortitis and endarteritis, with obliteration of the lumen of the innominate artery and partial obstruction of the lumen of the left subclavian artery.

Atheromatosis.—Cases of complete occlusion of great vessels at the aortic arch by atheromatosis must be uncommon. Galdston and co-workers [9c] reported two cases of common carotid artery thrombosis due to atherosclerosis, and Webster and co-workers [69] have described three such cases. Avery's case [70] showed only partial occlusion of the right arm vessel. Bittorf's case [18a] of involvement of all four vessels arising from the aortic arch was probably arteriosclerosis, in his opinion; from the evidence presented it must be considered obscure. In five cases in our series there was enfeeblement (but not obliteration) of pulses due probably to atheromatosis, but in only one was the pulse alteration marked. None of the five has been examined pathologically. In two cases there was complete obliteration of the left arm pulse (Cases 6 and 7 below), which developed under observation.

Atheromatosis may be a conspicuous contributing factor in the vascular occlusions of syphilitic aortitis and of those which seem to be related to trauma. Syphilitic aortitis renders the aortic arch more vulnerable to atheromatosis. Atheromatosis rarely is as marked in the aortic arch as in the abdominal aorta, except in the

62. Motley, L., and Moore, R.: Obliterating Syphilitic Arteritis, J. A. M. A. **100**:656, 1933.

63. Snow, N. L.: Syphilitic Degeneration of Arteries as a Cause of Aneurism: With a Report of 2 Cases, M. Rec, **18**:229, 1880.

64. Thompson, R. S.: Aneurysm of the Aorta with Early Pressure Symptoms and Obliteration of Left Carotid, Tr. Glasgow Path. & Clin. Soc. **4**:109, 1891-1893.

65. Barker, W. F.: Syphilitic Aortitis with Obstruction of Multiple Aortic Ostia. New England J. Med. **241**:524, 1949.

66. Riegel, F.: Berlin Klin. Wchnschr. **14**:300, 1877.

67. Pijoan de Beristain, C.: Disappearance of the Radial Pulse in Simple Syphilitic Aortitis. Semana méd. españ. **6**:178, 1943.

68. Casiello, A., and Hanono, M.: Absence of Pulse in the Upper Extremities and Right Carotid in Luetic Aortitis, Rev. méd. Rosario **34**:1159, 1944.

69. Webster, J. E.; Dolgoff, S., and Gurdjian, E. S.: Spontaneous Thrombosis of the Carotid Arteries in the Neck: Report of 4 Cases, Arch. Neurol. & Psychiat. **63**:942, 1950.

70. Avery, H.: Unequal Radial Pulses with Intermittent Claudication of the Right Leg, Proc. Roy. Soc. Med. **25**:804, 1932.

presence of preexisting syphilitic aortitis. In China, although syphilitic aortitis is common, the extensive atheromatosis of the intima associated with this lesion in this country is not seen.[71]

The following cases are believed to represent instances of the aortic arch syndrome due to atheromatosis. Even though not stated in the brief abstracts, other causes of aortic arch syndrome have been adequately excluded, in our opinion

CASE 1.—W. S. (J. H. H. 575724), a 56-year-old white man, was admitted for investigation of "low blood pressure" of 10 years' duration. There had been intermittent claudication of the legs for 10 years. Four years previously a mild cerebrovascular accident had occurred, and for a year there had been episodes of decreased vision, giddiness, and weakness on sudden changes of position or prolonged walking and standing. On examination no blood pressure was obtainable in three of the four extremities, with a value of 62/48 mm. in the left arm when the patient was recumbent. Even this could not be obtained when the patient stood. The left carotid pulse was not felt, although the right was forceful. There was attenuation of the smaller retinal arterioles with many hemorrhages and exudates. X-rays revealed a normal heart and aorta. An electrocardiogram showed changes consistent with old posterior myocardial infarction. Serological tests for syphilis were negative.

CASE 2.—J. F. (J. H. H. 170371) was a white woman with Leriche's syndrome,[72] which was fully developed when she was first observed at this hospital, in 1939, when she was 52 years old. The blood pressure in the right arm was 170/80 mm. Hg, and in the left arm 110/82, with barely palpable left radial pulse. By 1946 clear signs had developed of an aneurysm, presumably arteriosclerotic, of the abdominal aorta.

CASE 3.—J. P. (J. H. H. 184964), a white man born in 1905, was demonstrated by aortograms to have Leriche's syndrome of thrombotic occlusion of bifurcation of the aorta. Claudication began at age 32, and impotence in the form of inability to maintain a stable erection began at the age of 36 years. In 1951 the blood pressure in the right arm was 160/100 mm., and in the left arm 125/110. The left radial pulse was feeble. In the left supraclavicular fossa and to a lesser extent under the clavicle a rough systolic bruit was heard. The basis of the premature atheromatosis appeared to be idiopathic hypercholesterolemia; serum cholesterol levels were 355 to 422 mg. per 100 cc. and there were xanthelasmata of the upper eyelids. After the patient's close adherence to a low-fat diet for 28 months serum cholesterol levels fell to as low as 220 mg. and there was partial alleviation of symptoms in the lower part of the body; the pulse abnormality in the left arm remained unchanged.

CASE 4.—W. A. (J. H. H. 291541) was a 67-year-old white man with signs and symptoms attributable to generalized arteriosclerosis: vertigo, diplopia, and blurred vision from cerebral arteriosclerosis; absent pulses in the legs below the femorals; acute posterior myocardial infarction from coronary sclerosis. Several months before the coronary accident the blood pressure and pulse in the right arm were found to be unobtainable, the blood pressure in the left arm being 130/88 mm. Hg. Pulses in the carotid arteries were full and equal. X-ray of the chest even after the myocardial infarction showed the heart and aorta to be of normal size.

CASE 5.—J. McC. (J. H. H. 523086), a 62-year-old white man, complained only of low blood pressure in the left arm. Since infancy the pulse in the left arm had been said to be poor. In later years physicians remarked on the lower pressure in the left arm and there was an impression that the anisosphygmia was increasing. Examination showed moderate peripheral and retinal arteriosclerosis. The left common carotid artery and the arteries of the left arm pulsated much less vigorously than the corresponding ones on the right. The blood pressures were 160/90 (right arm) and 120/85 (left arm). By x-ray the heart was of normal size, with moderate dilatation of the arch of the aorta. Electocardiogram was consistent with right bundle branch block.

71. Dock, W.: Personal communication to the authors.

72. Leriche, R., and Morel, A.: The Syndrome of Thrombotic Obliteration of the Aortic Bifurcation, Ann. Surg. **127**:193, 1948.

CASE 6.—M. F. (J. H. H. 310324), a 59-year-old Negro woman with diabetes, had suffered multiple cerebral softenings as part of her general arteriosclerosis. Pulse and blood pressure were at first markedly diminished and after about six months were unobtainable in the left arm. Since there were no pulse abnormalities elsewhere (specifically, the left leg pulses were normal) and since some pulse change was present before the major neurologic changes had occurred, atheromatosis was considered the most likely cause.

CASE 7.—J. R. G. (J. H. H. 623487), a 56-year-old white man, had mild diabetes mellitus and classical intermittent claudication of the legs. No pedal pulses were palpable. When he was first seen a harsh systolic murmur was audible in a localized area at the base of the neck anteriorly on the left side. Four months later this murmur was no longer present and no pulses were palpable in the left arm. The brachial and radial arteries were very sclerotic in both arms. The patient now complained of "muscular pain" in the left arm, especially the biceps area, on use of the arm.

Atheromatosis is suggested as the etiology by the description of the necropsy findings in Broadbent's case.[73] This patient was a 50-year-old man who had had syphilis. Absence of pulses had been first detected after he had been thrown from a train in Boxmoor tunnel 30 years before. The findings at postmortem examination appear to have excluded syphilitic aortitis, since "very little disease was found in the internal coat of the ascending part of the arch, and the walls were perfectly elastic." The innominate artery was almost closed by an atheromatous plaque, as was also the left subclavian. This case may be similar to that of W. W., cited in detail as a case of obscure origin. In both speculation seems warranted as to the predisposition to atheromatosis resulting from trauma of special types.

Trauma with Aneurysm.—It is always difficult and hazardous to implicate remote or even recent trauma in conditions such as the one under discussion here. As seen above in the section on the clinical picture, trauma may have played a role in several of the syphilitic aortitis cases. Samson [74] presented two cases in which there was suggestive evidence that trauma precipitated dissecting aneurysm of the aorta. Warfield [75] reported a case in which dissecting aneurysm of the aorta developed following chest trauma in an automobile accident. Huebener's case [76] was one of saccular aneurysm of the ascending aorta presumably due to trauma. Warfield [75] states that the first case of traumatic aneurysm was reported by Testa in 1813. As in the early cases of Moxon [77] and Albutt,[78] the relationship of trauma to the aneurysm is circumstantial. Shennan [79] described a case in which a false aneurysm developed in the aortic wall in the region of the left subclavian artery and the ligamentum arteriosum following trauma. Pulse changes were not noted in this patient. An important point illustrated by many of these cases is that the

73. Broadbent, W. H.: Absence of Pulsation in Both Radial Arteries, the Vessels Being Full of Blood, Tr. Clin. Soc., London, **8**:165, 1875.

74. Samson, P. C.: Dissecting Aneurysms of the Aorta, Including the Traumatic Type: 3 Case Reports, Ann. Int. Med. **5**:117, 1931-1932.

75. Warfield, L. M.: Injuries to the Heart and Aorta, Wisconsin M. J. **32**:688, 1933.

76. Huebener, W.: Traumatic Causation of Aortic Aneurysm, Monatsschr. Unfallh. **35**:342, 1928.

77. Moxon: Aneurysm Opening into the Left Bronchus Avoiding the Recurrent Nerve, Wholly Without Spasmodic Symptoms, Med. Times & Gaz. **2**:95, 1870.

78. Albutt, T. C.: The Effects of Overwork and Strain on the Heart and Great Blood Vessels, St. George's Hosp. Rep. **5**:23, 1870.

79. Shennan, T.: Traumatic (False) Aneurysm of the Aorta, J. Path. & Bact. **32**:795, 1929.

aorta in the vicinity of the left subclavian ostium is the portion most liable to injury from indirect trauma.[80] In the following case there is evidence of relationship of trauma to the aortic aneurysm and the pulse changes present:

C. C. (J. H. H. 574668), a 48-year-old white female nurse, was admitted to the service of Dr. H. William Scott on June 7, 1951, for study of an aortic aneurysm, which apparently developed following an automobile accident.

She never had syphilis or any symptoms referable to the cardiovascular system. On Oct. 1, 1950, she was severely injured in an automobile accident. She was knocked unconscious and had no memory of events in the few days following the accident. However, she sustained fractures of several ribs and the first lumbar vertebra. When she first regained consciousness she was aware of pain in her back and chest and had trouble breathing. The family noticed hoarseness within 48 hours of the accident. She was discharged from the hospital after two weeks. The pain in the chest persisted, however, and there was progression of the hoarseness during the next few weeks. Late in November 1950 x-rays of the chest were again made and a pulsating mass in the upper mediastinum was discovered.

The principal finding on physical examination was a palpable weakness of the left radial pulse, with a blood pressure of 135/80 mm. in the right arm, 90/80 mm. in the left. The carotid pulses were full and equal. The left vocal cord was paralyzed.

Serological tests for syphilis were negative. On fluoroscopy an orange-sized mass with expansile pulsations was seen in the left upper mediastinum in the region of the aortic knob. Angiocardiograms revealed filling of the mass with contrast substance. Whether the aneurysm arose directly from the aorta or from the left carotid or left subclavian arteries could not be determined.

On July 19, 1951, thoracotomy was performed by Dr. Scott. The dissection was difficult. The aneurysm appeared to arise from the aorta at the mouth of the left subclavian artery. Its mouth was rather wide, involving the first part of that vessel as well as that part of the transverse aortic arch between the left common carotid artery and the left subclavian artery. The aneurysm was wrapped with reactive polyethylene film. About one month after the operation the patient's voice had returned to normal. Five months after operation pulsations in the aneurysm were seen by fluoroscopy to be diminished. Six months after operation hoarseness returned and the patient began to have much left upper chest pain. On Oct. 4, 1952, thoracotomy was performed by Dr. Henry T. Bahnson and it was possible to resect the aneurysm in toto, sacrificing the left subclavian artery. A shearing type of injury was probably responsible for localization of the major damage at the site described.

We have seen one other case of traumatic or false aneurysm of the aortic arch. Although there were no pulse changes, this patient (J. H. H. 379861) was in an automobile accident in which not only did the steering wheel hit his upper chest but also his head was thrown back in hyperextension. Seven years after the accident he (then 26 years old) was found to have a calcified saccular aneurysm of the aorta, with its mouth just beyond that of the left subclavian artery. Since the patient had had hemoptyses related probably to the aneurysm, wiring was performed, and the patient has had no trouble since that time.

Numerous cases are on record[81] in which a previously normal aorta has been torn open or completely severed in victims of accidents which produce little external

80. Fidler, H. K.: Traumatic Rupture of the Thoracic Aorta, Canad. M. A. J. **60**:590, 1949.

81. (*a*) Copeland, G. G.: Traumatic Rupture of the Healthy Aorta Without External Signs of the Cause of Death, J. A. M. A. **63**:1950, 1914. (*b*) McDonald, J. B., and Campbell, W. A.: Traumatic Rupture in the Normal Aorta in Young Adults: Report of 2 Cases, Am. Heart J. **30**:321, 1945. (*c*) Spicer, F. W.: Trauma and Internal Disease, Philadelphia, J. B. Lippincott Company, 1939. (*d*) Stern, R. A.: Trauma in Internal Disease, New York, Grune & Stratton, Inc., 1945, p. 159.

evidence of trauma. Hass [82] made similar observations in victims of aircraft accidents. Wilson [83] described pathological findings in 12 persons killed by blast when a bomb exploded in a rock-walled shelter. In one case, that of a 25-year-old woman, a transverse tear was found in the aortic arch ½ in. (1 cm.) distal to the aortic cusp. "The wall of the ascending aorta was infiltrated with blood and inferiorly the infiltration extended into the pericardial sac." If the rupture into the pericardial sac had not occurred, this patient might have lived and an aneurysm and/or occlusion of great vessels from the arch might have developed. These observations are based entirely on postmortem examination; no cases of survival with proved cardiac or aortic damage have, to our knowledge, been reported. It is not inconceivable that injury to the aortic wall of a lesser degree might result in intimal tears and that these tears might later initiate dissection of vessel ostia or be a nidus for atheromata encroaching on the vascular lumen. Thrombosis of the iliac artery has been caused by abdominal contusion,[81d] and traumatic thrombosis of peripheral vessels, including the carotid arteries, is still commoner.[84] Such, it would seem, might occur at the branches of the aortic arch. A predilection for the development of atherosclerosis at sites of trauma to arteries of types including stretching has had good experimental analogy in the work of Ssolowjew.[85]

Trauma Without Aneurysm.—In the cases of W. W. (p. 706) and W. B. (p. 715) and in the case of Broadbent,[73] trauma may have played a supporting role in the development of the pulse changes. In both trauma may have hastened the development of atheromatosis at the vessel ostia. In the case of W. B., a probable instance of syphilitic aortitis without aneurysm, symptoms had their onset after trauma although pulse changes had been observed before.

We have recently had the opportunity to see a patient (J. H. H. 618679) with syphilis in whom thrombosis of the common carotid artery occurred shortly after the head had been held in a hyperextended position for a prolonged period of time for dental extractions. Pain in the right eye was noted within a few hours, and the following morning the patient was blind in the right eye, with hemiplegia on the left. Two months later there was right optic atrophy and absence of the right carotid pulse. There was no evidence of aortitis. The probable diagnosis was considered to be syphilitic arteritis with thrombosis precipitated by trauma to the vessel.

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82. Hass, G. M.: Safety in the Design of Aircraft, J. Aviation Med. **15**:395, 1944; Types of Internal Injuries of Personnel Involved in Aircraft Accidents, ibid. **15**:77, 1944; Internal Injuries of Personnel Involved in Aircraft Accidents, Air Surgeons Bull. **1**:5, 1944; personal communication to the authors.

83. Wilson, J. V., and Tunbridge, R. E.: Pathological Findings in a Series of Blast Injuries. Lancet **1**:257, 1943.

84. (*a*) Caldwell, J. A.: Post Traumatic Thrombosis of the Internal Carotid Artery, Am. J. Surg. **32**:522, 1936. (*b*) Dodd, H.: Gangrene Following Fractures: Excluding Gas Gangrene, Brit. J. Surg. **22**:246, 1934. (*c*) Lawrence, K. B.; Shefts, L. M., and McDaniel, J. R.: Wounds of the Common Carotid Arteries: Report of 17 Cases from World War II, Am. J. Surg. **76**:29, 1948. (*d*) Hunt.[9d]

85. Ssolowjew, A.: Experimental Studies of Hypercholesterolemia, Virchows Arch. path. Anat. **245**:203, 1923. Ssolowjew.[84]

Leriche [86] has described a case in which the fracture of the inner end of the left clavicle at age 6 was followed by the development of a Raynaud-like syndrome at age 46. The patient was a school teacher who had difficulty writing on the blackboard with her left arm and much pain in the arm at night. Operation revealed complete occlusion of the prescalenus portion of the subclavian artery. Removal of this segment resulted in complete relief of symptoms, and the patient was well 30 years later. It would seem possible that trauma produced changes which predisposed the vessel to premature atheromatosis and thrombosis.

The case of Guthrie and Mayou [87] reported in 1908 may represent an instance of traumatic occlusion without aneurysm formation, although the details are meager. The patient, a boy of 7, was run over by a cab, with resulting cerebral concussion and multiple rib fractures on the left. Six days after the accident he became aphasic, paralyzed on the right side, and blind in the left eye. Five months after the accident there was atrophy of the left optic nerve and complete absence of pulsation in the left common carotid artery.

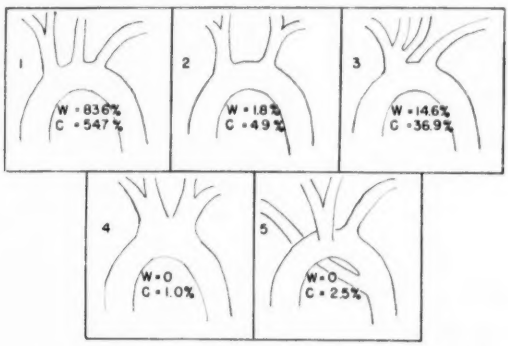

Fig. 3.—Five general varieties of aortic arch branching (adapted from De Garis [89]). W indicates whites; C, Negroes. The figures given are percentages of the total racial group.

Congenital Anomalies.—The mode of origin of the great vessels from the arch is more variable than one might think. Figure 3 is a diagrammatic presentation of the approximate incidence of each of the commoner varieties of aortic arches.[88] The statistics are adapted from the data of DeGaris and co-workers,[89] who studied specimens from 110 whites and 203 Negroes. For clinical purposes the classification indicated in the diagram is adequate, in our opinion. It accounts for the origin of the four arteries whose pulsations are determined clinically. Further variations on these five basic patterns have been described and involve peculiarities in the origin

86. Leriche, R.: Influence of Obliteration of the Subclavian Artery on Peripheral Vasoconstriction: Onset of a Syndrome Resembling Raynaud's Disease, Angiology **3**:380, 1952.

87. Guthrie, L. G., and Mayou, S.: Right Hemiplegia and Atrophy of Left Optic Nerve, Proc. Roy. Soc. Med. **1**:180, 1908.

88. The varieties of aortic arch indicated in Figure 3 are not congenital anomalies in a class with coarctation of the aorta or patent ductus arteriosus. They are inherited differences. The difference in incidence in Negro and white groups is worthy of note.

89. De Garis, C. F.; Black, I. N., and Riemenschneider, E. A.: Patterns of the Aortic Arch in American White and Negro Stocks: With Comparative Notes on Certain Other Mammals, J. Anat. **67**:599, 1932-1933.

of the left vertebral artery and the thyroid ima artery (from the aortic arch). These are not pertinent to the present problem. We have grouped together cases in which two vessels arise from the arch by a distinct common trunk (truncus communis) and those cases in which the same two vessels arise from the arch merely by a common ostium (radix communis). Clinically and pathologically this grouping seems justified, since it is likely that in either case flow through the two vessels involved will be about equally impeded.

Type 1 of Figure 3 is the common variety of aortic arch. In Types 2, 3, and 4 there can be seen a tendency to clumping of the arterial stems at the aortic arch. Aortic arch Type 5 is unique in that the right subclavian artery arises separately from the left side on the dorsal aspect of the aorta at the junction of the transverse and descending portions.[90] The embryological background of this anomaly, which occurred in 2.5% of Negroes in DeGaris' series, has been presented elsewhere[91] (the occurrence of this anomaly in no whites in DeGaris' series is undoubtedly chance, since it has been reported many times in whites by others[90b]).

Many of the patients mentioned in previous sections of this paper were found at postmortem examination to have anomalous aortic arches. Kampmeier and Neumann[46] were the first to suggest that congenital variation might contribute to vascular occlusion in aneurysm of the aorta. It seems likely that anomalous placement of vessels may render them more susceptible to occlusion from any of the causes previously mentioned. In several of the cases presented above a congenital factor has been suspected, and in six cases variations from the normal have been demonstrated at postmortem examination. The cases of Broadbent,[78] Barker,[68] and Darling[49] (Cases 2 and 3) demonstrated variation in the interrelationships of the right subclavian, right carotid, and left carotid arteries. In Broadbent's case the orifices of the innominate and left carotid arteries were described as unusually close together. Barker's case demonstrated a similar situation, in that the innominate and left common carotid arteries arose in close proximity. An apparently unusual situation was seen in Darling's Case 2, in that the "right subclavian and carotid arteries arose almost simultaneously from the arch so that there was almost nothing to represent the innominate artery." The mouth of the "innominate" had a "double barrel" appearance (radix communis). In Darling's case and Penzoldt's[92] Case 2 the left common carotid artery arose from the innominate artery a few millimeters above its aortic orifice, as in Type 3, Figure 3. Consequently the arterial supply to the head and arms left the aorta through two rather than the usual three primary orifices. A similar reduction to two ostia by a different mechanism was demonstrated in the case of Cohen and Davie.[47] In their case the origins of the left common carotid and left subclavian arteries were combined as in Type 2 of Figure 3. Penzoldt's[92] Case 1 represents an instance of right carotid occlusion in the most unusual aortic arch type (Type 5). Variations in the origin of the left vertebral artery were described in the case of Broadbent and that of Darling (Case IV). In Broadbent's case

90. (*a*) Herrick, A. B.: A Rare Anomaly of the Arch of the Aorta: With an Additional Muscle in the Neck, Bull. Johns Hopkins Hosp. **8**:234, 1897. (*b*) Segers, M.: Left Insertion of the Right Subclavian Artery, Acta cardiol. **5**:182, 1950.

91. De Garis, C. F.: Anomalous Axillary Collaterals and the Pattern of Arm Arteries in Anomalous Right Subclavian Arteries, Am. J. Anat. **51**:189, 1932.

92. Penzoldt, F.: Thrombosis (Autochthonous or Embolic) of the Carotid, Deutches Arch klin. Med. **28**:80, 1881.

the left vertebral instead of arising from the subclavian, sprang from the arch of the aorta close to the origin of the subclavian, the orifice of which was narrowed to the size of a crow quill by the proximity of the vertebral.

In Darling's Case 4 the left vertebral artery came directly from the aorta. The diagram illustrating Barkér's case [65] shows a vessel arising from the arch between the left common carotid and the left subclavian arteries. Though no mention is made of this vessel, it could be assumed that it is the left vertebral artery. It seems more than coincidence that so many of these instances of the aortic arch syndrome involved less common varieties of aortic arches. It has been suggested [23a] that the development of the aortic arch and its branches in some of these patients was like that of the horse, in which a single trunk (truncus brachiocephalicus communis) arises from the aortic arch and later divides into the four vessels supplying the upper part of the body.[93] Congenital stenosis or atresia or acquired obstruction of this trunk might then produce a complete aortic arch syndrome. We mention this in passing only to point out that we know of no such case and believe that this explanation, though intriguing, is entirely fanciful.

Not pertinent to this review are congenital anomalies of the aortic arch which do not primarily concern the main arterial branches, e. g., aortic rings, right aortic arch, etc., since pulse change is not a characteristic of these anomalies.[94]

Just as there is wide variation in the anatomical structure of the normal aortic arch, so there may be wide variation between the blood pressures in the two arms in apparently normal persons. The magnitude of this variation as described by Rueger [95] and Korns and Guinand [96] should be considered in the evaluation of pulse differences.

The true congenital anomalies of the aortic arch, specifically coarctation and patent ductus arteriosus, may produce pulse differences. Cases of weak or absent pulses in the left arm in association with coarctation of the aorta have been reported by a number of writers.[97] Asymmetrical development of the upper extremities may be found, and the collaterals and rib notching may be absent or relatively inconspicuous on the left. The cause of the pulse abnormality in the left arm may be stenosis of the ostium of the left subclavian artery,[98] atresia of the proximal seg-

93. Sisson, S., and Grossman, J. D.: The Anatomy of Domestic Animals, Ed. 3, Philadelphia, W. B. Saunders Company, 1938, p. 643.

94. Edwards, J. E.: Anomalies of the Derivatives of the Aortic Arch System, M. Clin. North America **32**:925, 1948.

95. Rueger, M. J.: Blood Pressure Variations in the 2 Arms, Ann. Int. Med. **35**:1023, 1951.

96. Korns, H. M., and Guinand, P. H.: Inequality of Blood Pressure in the Brachial Arteries with Special Reference to Disease of the Arch of the Aorta, J. Clin. Invest. **12**:143, 1933.

97. Bayley, R. H., and Holovbek, J. E.: Coarctation of the Aorta at or Above the Origin of the Left Subclavian Artery, Brit. Heart J. **2**:208, 1940. Brown, A.: Congenital Stenosis of the Aorta, Lancet **1**:1719, 1912. Schwartz, S. P., and Greene, D.: Coarctation of the Aorta in Children: The Syndrome of Constriction of the Isthmus of the Aorta, with Involvement of the Origin of the Left Clavian Artery, Am. Heart J. **23**:99, 1942. Hills, R. G.: Coarctation of the Aorta with Unequal Blood Pressures in the Arms, Bull. Johns Hopkins Hosp. **62**:475, 1938. King, J. T.: The Blood Pressure in Stenosis at the Isthmus (Coarctation) of the Aorta: Case Reports, Ann. Int. Med. **10**:1802, 1937.

98. Bauer, D. F., and Iverson, L.: Coarctation of the Aorta: Report of 2 Cases; Relating Clinical Data to Degree of Constriction Measured at Autopsy; With a Method of Standardization for Related Measurement, Am. Heart J. **30**:30, 1945.

ment of the subclavian artery,[99] or origin of the left subclavian artery beyond the coarctation.[100] In a group of 125 cases recently studied at operation and/or autopsy in this hospital the left subclavian artery arose below the coarctation in 1 and in 3 others there was marked narrowing or obliteration of this artery.[101]

As we have pointed out repeatedly, a combination of etiologic factors may be operative in cases of the aortic arch syndrome. In a 44-year-old man (J. H. H. 408041) syphilitic aortitis was thought to participate with the congenital factor (coarctation of the aorta) in the production of left subclavian artery occlusion which progressed to completeness during a period of several months' observation. A similar case has been reported.[102]

Taylor and Pollock[103] recently described two patients, brother and sister, with a variety of coarctation, or stenosis, of the aorta, which appears, from study of the one which came to postmortem examination, to involve the aorta from a point immediately above the aortic cusps to a point just beyond the origin of the left subclavian artery. In the case in which autopsy was performed the lumen was reduced to a diameter of 3 mm. in the stenotic segment, and the aorta appeared normal beyond the origin of the left subclavian artery. Blood pressures were about equally reduced in all four extremities, being only 86/78 mm. Hg in the left arm in one case. The distribution of the systolic murmur and thrill resembled that of aortic stenosis more than that of classic coarctation. No arterial collaterals or rib notching was identified. The mother of these two patients appeared to have classical stenosis of the aortic isthmus.

Instances of pulse abnormality in the right arm in association with coarctation have been described by Fawcett (Case 10),[104] East,[105] Love and Holms,[106] Espinosa,[107] and Stephens (cited by Gross[108]). In East's patient the blood pressures were 135/100 and 195/145 mm. Hg in the right and left arms, respectively, but no autopsy information was available. In the case reported by Love and Holms, blood pressures were 150/90 and 210/95 mm. Hg in the right and left arms, respectively, with a noticeable difference in the radial pulses of the two arms. The coarctation was not recognized before death. Anatomical studies revealed that in addition to coarcta-

99. Woltman, H., and Sheldon, W. D.: Neurologic Complications Associated with Congenital Stenosis of Isthmus of Aorta: Case of Cerebral Aneurysm with Rupture and Case of Intermittent Lameness Presumably Related to Stenosis of Isthmus, Arch. Neurol. & Psychiat. **17**:303, 1927.

100. Evans, W.: Congenital Stenosis (Coarctation), Atresia, and Interruption of the Aortic Arch (a Study of 28 Cases), Quart. J. Med. **2**:1, 1933. Parker, R. L., and Dry, T. J.: Coarctation of the Aorta at an Unusual Site Associated with a Congenitally Bicuspid Aortic Valve, Am. Heart J. **15**:739, 1938.

101. Sloan, R. D.: Personal communication to the authors.

102. Moniz de Beltencourt, J.; Geraldes Barba, F., and Polonio, P.: Coarctation of the Aorta and Opening of the Left Subclavian Artery, Amatus Lusitanus **1**:392, 1942.

103. Taylor, R. R., and Pollock, B. E.: Coarctation of the Aorta in 3 Members of a Family, Am. Heart J. **45**:470, 1953.

104. Fawcett, J.: Coarctation of the Aorta: As Illustrated by Cases from the Postmortem Records of Guy's Hospital from 1826 to 1902, Guy's Hosp. Rep. **59**:1, 1905.

105. East, T.: Coarctation of the Aorta, Proc. Roy. Soc. Med. **25**:796, 1932.

106. Love, W. S., and Holms, J. H.: Coarctation of the Aorta with Associated Stenosis of the Right Subclavian Artery, Am. Heart J. **17**:628, 1939.

107. Espinosa, O. H.: Coarctation Combined with Probable Anomaly at Point of Origin of the Right Subclavian, Rev. argent. cardiol. **15**:68, 1948.

108. Gross, R. E.: Coarctation of the Aorta: Surgical Treatment of 100 Cases, Circulation **1**:41, 1950.

tion there was marked stricture of the right subclavian artery at its origin from the innominate artery (well illustrated by the authors). Very little collateral circulation was found on the right side although there were well developed collaterals on the left. In a recently reported case both subclavian arteries arose beyond the coarctation (which was located in the usual position), and all four extremities were pulseless.[109] Both carotid arteries arose directly from the aorta. Basically this should be considered a Type 5 aortic arch with superimposed coarctation.

Grishman, Sussman, and Steinberg [110] called attention to an important group of patients (they reported three cases) who have absent or much diminished pulses in the left arm and in some in the left carotid artery, presumably on a congenital basis. They expressed the opinion that these represented atypical (perhaps forme fruste) cases of coarctation. There was no discrepancy between arm and leg pressures in their cases and the angiocardiograms were unconvincing. It is a common finding to have some indentation of the aorta at the attachment of the ligamentum arteriosum.

It has been said [111] that in cases of patent ductus arteriosus occasionally there are unequal radial pulses, with a higher blood pressure in the right arm than in the left. Some of the cases on which this statement was based may have been instances of the fetal type of coarctation with patent ductus and stenosis of the left subclavian ostium. Oda [87a] found a lower blood pressure in the left arm in all of seven cases of patent ductus studied. This discrepancy he attributed to dissipation of pressure into the pulmonary artery. As described later, some patients with the aortic arch syndrome may have machinery murmurs; in some of the so-called cases of patent ductus with absent pulses there may actually be a purer variety of aortic arch syndrome.

In our case review we have repeatedly seen "congenital anomaly" invoked as an explanation for absent pulses. It should be emphasized that while congenital variation may be an underlying contributing factor it is rarely the primary cause of pulselessness. Sir Thomas Lewis [7] summarized the status of congenital factors in the causation of the aortic arch syndrome in this way:

> No such anomaly is known in which all of the usual vessels, innominate, subclavian, and carotid, fail; or which would account for loss of pulses in head, neck, and arms. The congenital anomalies of arteries are not suppressions of arterial supply, they are merely unusual arrangements of supply.

Chronic Dissection of the Aorta.—Healed dissected aneurysm of the aorta undoubtedly can account for pulse differences such as those under consideration. Shennan,[112] in his review of 300 cases, states that inequalities of the radial pulses are described in old dissecting aneurysms but does not stress this as a prominent feature. Baer and Goldburgh [113] in reviewing 44 cases of dissecting aneurysm

109. McGregor, M., and Melalie, M.: Coarctation of the Aorta, Brit. Heart J. **14**:531, 1952.

110. Grishman, A.; Sussman, M. K., and Steinberg, M. F.: Atypical Coarctation of the Aorta with Absence of the Left Radial Pulse, Am. Heart J. **27**:216, 1944.

111. Vaquez, H.: Disease of the Heart, translated and edited by G. F. Laidlaw, Philadelphia, W. B. Saunders Company, 1924, p. 189. Friedberg, C. K.: Diseases of the Heart, Philadelphia, W. B. Saunders Company, 1950, p. 660.

112. Shennan, T.: Dissecting Aneurysm, National Research Council, Special Report Series, No. 193, London, His Majesty's Stationery Office, 1934.

113. Baer, S., and Goldburgh, H. L.: The Varied Clinical Syndromes Produced by Dissecting Aneurysm, Am. Heart J. **35**:198, 1948.

found only 1 with absent radial pulse. Todd,[114] in 1844, reported a patient with dissecting aneurysm, living 11 days after onset, in whom enfeeblement of the right radial pulse was a striking feature. The pathogenesis of occlusion in this disease is well illustrated by a published case [115] in which the innominate artery was completely occluded by dissection and inward bulging of the intima. Vessels may be dissected for a considerable distance from the aortic arch; the occlusion may be so remote from the origin of the vessel that the process may be mistaken for embolism.

The second case of Mote and Carr [116] serves well as an example of pulse difference due to a healed dissection of the aorta. In a woman 32 years of age sudden severe substernal pain radiating to the neck and back developed on Oct. 1, 1937. On examination systolic and diastolic aortic murmurs were heard. The radial and brachial pulses on the right were smaller than on the left. Pulsation in the right carotid was also markedly diminished. Blood pressure was 130/0 mm. Hg in the left arm, 80/60 in the right arm, and 160/0 in both legs. The blood pressure stabilized at 120/30 mm. Hg on the left and 70/60 mm. Hg on the right. Pulsation became almost imperceptible in the right carotid artery and diminished in the left. The patient noted transient episodes of decreased visual acuity. The patient died on Aug. 8, 1940, two years and 10 months after the onset of dissection. At postmortem examination the

proximal 5 cm. of the aortic arch were dilated and formed a sacculation in the right and anterior aortic wall which projected forward and laterally to the right in a large, round knob about 8 cm. in diameter. This formation extended to the innominate artery and exerted considerable pressure upon it externally. There was a tear in the anterior wall of the aorta 3.5 cm. above the aortic ring which formed the entrance to an artificial channel which extended to the aortic bifurcation and had dissected into the left carotid artery.

Thrombophilia.—Aggeler, Lucia, and Thompson [15] described a case of absent pulsation in all the arteries of the upper extremities and neck. The etiology of the vascular occlusions remained obscure, but it was suggested that thrombocytosis might have been a contributing factor. Nygaard and Brown [117] in their review of five cases of essential thrombophilia, reported one case in which the brachial, radial, and ulnar pulses were absent in one arm. In this case the etiology was not at all clear, and it is possible that embolism may have been the cause of the occlusion.

The case of Aggeler, Lucia, and Thompson is an excellent example of the aortic arch syndrome, whatever the etiology, and is abstracted here.

About 1936, at the age of 25, a Spanish woman had suddenly fallen to the floor, and following this incident she had become progressively weakened, with cold hands and feet. She noted dizziness on arising quickly from the supine position. Her memory was markedly impaired for both recent and remote events. In 1931 her blood pressure had been 120/70, and in July 1937 it was 100/60. In Novem-

114. Todd, R. B.: Account of a Case of a Dissecting Aneurysm of the Aorta, Innominata and Right Carotid Arteries, Giving Rise to Suppression of Urine and White Softening of the Brain, M. Clin. Tr. **27**:301, 1844.

115. Cabot Case 37112, New England J. Med. **244**:412, 1951.

116. Mote, C. D., and Carr, J. L.: Dissecting Aneurysm of the Aorta, Am. Heart J. **24**:69, 1942.

117. Nygaard, K. K., and Brown, A. E.: Essential Thrombophilia: Report of 5 Cases, Arch. Int. Med. **59**:82, 1937.

ber 1938 no blood pressure could be measured in either arm and the radial pulses were not palpable. The blood pressure in the legs was 160 to 170 mm. systolic, with indefinite diastolic readings. The carotid pulse was palpated on the right but not on the left. A strong pulsation was present in the suprasternal notch. A loud to-and-fro murmur transmitted to the neck was heard over the left sternoclavicular region, left supraclavicular area, and left second intercostal space.

Studies in 1940 revealed the following abnormalities: Slit lamp examination of the conjunctivae showed clumps of erythrocytes traveling as units in the larger vessels. Ophthalmoscopic examination of the right eye revealed an atrophic optic nerve head and many occluded and obliterated arterioles. There were large areas of retinal hemorrhage. Laboratory examination revealed hemoglobin 9.6 gm. per 100 cc.; red cell count 4,400,000 per cubic millimeter; white cells 8,900 per cubic millimeter. Ten platelet counts varied between 1,200,000 and 1,500,000 per cubic millimeter. Sternal marrow biopsy revealed hyperplasia of both myeloid and erythropoietic series and an increased number of megakaryocytes. Autoagglutination of erythrocytes occurred at body, room and ice-box temperatures. Kolmer and Kahn tests were negative. Biopsy of an artery 2 mm. in diameter, in the usual location of the right brachial artery, revealed normal findings. X-ray and fluoroscopic examination of the chest revealed normal heart and aorta, with no abnormal pulsations.

In 1941 the patient was complaining of increasing weakness, frequent headaches, and occasional nervous spells. Her nose had become tender, and two weeks before entry the bridge had collapsed, producing a saddle deformity. The right eye showed an old retinitis proliferans, with new-formed vessels and partial detachment of the retina. The cardiac murmurs previously described were inaudible. Diodrast angiocardiograms revealed no abnormalities of the heart or aorta itself. Two platelet counts were 820,000 and 890,000 per cubic millimeter. Unfortunately, at present writing follow-up of this patient has been impossible.

In their summary the authors discuss the thrombocytosis and autohemagglutination and reach the following conclusion:

> Because of the localization of the occlusive process to the large vessels arising from the arch of the aorta, it seems unlikely that changes in the blood plasma or an increase in the number of circulating blood platelets could have been entirely responsible for this condition. The etiology in our patient therefore remains obscure.

Many features of this case resemble those of the "young female" arteritis syndrome, which will be described subsequently.

Nonsyphilitic Arteritis.—There are a number of cases reported in which obstruction of the large branches of the aortic arch at their origin was part of a generalized arteritis. In most of these cases the exact nature of the arteritis is obscure. Buerger's disease, polyarteritis nodosa, and temporal ("giant cell") arteritis suggest themselves as possibilities.

The following case, which was studied in detail clinically and pathologically at this hospital, was previously reported [118] as a case of Buerger's disease. A restudy of the clinical picture and pathological material provides no unequivocal conclusion as to the nature of the vascular disease.

118. Lewis, D.: Spontaneous Gangrene of the Extremities, Arch. Surg. **15**:613, 1927.

W. W. (J. H. H. 198291), a plumber of German extraction, had onset of progressive intermittent claudication in the legs at the age of 40. He smoked a pack of cigarettes a day. At the age of 47 he was admitted to the hospital, where it was found that there were no pulses not only in both legs but also in the right arm. The blood pressure in the left arm was 130/90. Carotid pulses were felt only with difficulty. While in the hospital the patient had a left-sided convulsion followed by one on the right side, bilateral paralysis, and death. Postmortem examination revealed thrombotic occlusions of the aorta from the celiac axis to the bifurcation, with extension of the occluding process into the iliac arteries. All the main branches of the arch of the aorta showed pronounced sclerotic changes. The second portion of the right subclavian artery was occluded, and there were separate thrombotic occlusions of both the internal and the external carotid arteries on the right. Microscopic study of the blood vessels showed thickening of the intima, organized and partly recanalized thrombi with nonstaining pigment, and in places enormous amounts of fat in phagocytes, but there were no striking inflammatory changes. The arteries and veins were not bound together as in Buerger's disease. Although there was no calcification, cholesterol crystals were in abundance in places.

By definition this case represents Leriche's syndrome with certain additional features referable to changes in the upper portion of the body. The case resembles those of J. F. and J. P., described in the section on atheromatosis. Atheromatosis must be considered a very likely basis for the changes. Serum cholesterol determinations might have shed light on the nature of the process.

The pathological studies in cases reported by Gilmour,[119] Sproul,[120] and Jennings[121] are detailed enough to permit their classification as giant-cell arteritis, or temporal arteritis, to which there were also clinical evidences of alliance. Of Gilmour's four cases, in two there was involvement of both common carotid arteries and the left subclavian artery and in one there was involvement of the innominate artery. In Sproul's case, clinical notes are unavailable; however, "all the main branches were narrowed" and "histological study revealed a profound change affecting the aorta as well as the carotid, innominate, and subclavian arteries." In Jenning's case there were a weaker pulse and lower blood pressure in the left arm. The patient had had central retinal artery thrombosis, arthritis, temporal arteritis, diarrhea, urinary sediment changes, and leucocytosis. A pathologist reported, in reference to a biopsy of the temporal artery, that "polyarteritis nodosa is not excluded by the appearances." Cooke and co-workers[122] described involvement of the aorta, radial, and subclavian arteries but no occlusion of these vessels near their origin. The development of thrombosis is easily envisaged, however.

Harbitz[13] and Raeder[123] separately reported the remarkable case of arteritis involving the great vessels at the aortic arch. This case of arteritis in a young woman is the first of a series of cases collected by Frøvig (see below). We find it convenient to refer to this group as the "young female arteritis" variety of the aortic arch syndrome.

A 37-year-old woman was well until the spring of 1923, when "glittering" before her eyes developed. At Christmas, 1923, she had an attack of dizziness

119. Gilmour, J. R.: Giant-Cell Chronic Arteritis, J. Path. & Bact. **53**:263, 1941.

120. Sproul, E. E.: A Case of Temporal Arteritis, New York J. Med. **42**:345, 1942.

121. Jennings, G. H.: Arteritis of the Temporal Vessels, Lancet **1**:424, 1938.

122. Cooke, W. T.; Cloake, P. C. P.; Govan, A. D. T., and Colbeck, J. C.: Temporal Arteritis: A Generalized Vascular Disease, Quart. J. Med. **15**:47, 1946.

123. Raeder, J. G.: A Case of Symmetrical Affection of the Carotid with Presenile Cataract and Glaucoma as Well as Cerebral Atrophy, Klin. Monatsbl. Augenh. **78(Supp.)**:63, 1927.

associated with visual symptoms and jerking of the arms and legs. An ulcer appeared in the nose and extended through the septum, resulting in perforation. In the spring of 1924 weakness developed in the left arm and leg.

At the time of admission, in June 1924, no definite radial pulses could be felt. In August the patient had a transitory paresis of the left arm, and by October definite atrophy of the right half of the face and a cataract in the right eye had developed. Ophthalmoscopic examination revealed large dilated veins, irregular arteries, and a few grayish-white flecks around the macula. On Dec. 12, 1924, paralysis of the right arm and leg developed and the patient died a few days later.

At postmortem examination the ascending aorta was soft and elastic. The innominate artery was narrower than usual at its origin, and at a point 1.5 cm. above the origin the lumen admitted only a small probe. The walls were definitely thicker than normal. The right carotid and right subclavian arteries were completely obliterated, thin and narrow, and were filled by a grayish thrombus, which extended into the internal carotid artery, leaving the external carotid artery open. The left common carotid artery was obliterated completely from its origin to the internal carotid artery, which was thrombosed, while the left vertebral artery was partially occluded at its origin. The left subclavian artery was also obliterated, about 1.5 cm. above its origin, and was filled with thrombus for about 1 cm.

Histologically "the left common carotid artery showed fibrous thickening with large inflammatory infiltrations along the vasa vasorum; the infiltrations consisted of lymphocytes and did not contain giant cells." The other thrombosed vessels showed similar changes, as did the wall of the thoracic aorta.

Frøvig[3] reported a very significant case. In a 21-year-old woman "curious sensations" developed in the right arm in the summer of 1942. Subsequently episodes of weakness developed in the right leg, and eventually paralysis of the right arm and leg accompained by aphasia developed, from which she recovered rapidly but not completely. In February 1943 there were manifestations referable to the left arm and leg. In October 1943 a cataract developed rapidly in the right eye. Changes developed less rapidly in the lens of the other eye. The eyes also showed atrophy of the iris and spasm of the retinal vessels. The blood pressure in the lower limbs varied between 170/100 and 230/150. No pulsations were felt in the arms or neck. The carotid arteries were exposed for arteriography and found to be obliterated; a section was excised for pathological examination. The pathologist reported that

> the picture most resembles that of endarteritis productiva proliferans (secondary closure process). There is very little inflammation, mainly a closure process with organization (without evidence of a primary thrombus). It does not resemble peri-arteritis nodosa, nor rheumatic or syphilitic arteritis. Only in certain features does it resemble thromboangiitis obliterans.

Frøvig reviewed the literature and found four similar cases, that of Harbitz,[13] already mentioned, and those of Marinesco and Kreindler,[12c] Oota,[31] and Takahasi.[37b] He points out that all these patients were young women between the ages of 20 and 35 years. All showed cerebral and ocular manifestations, facial atrophy, and hypertension in the legs with absence of pulsation in the arteries of the arms and neck. Aggeler's case,[15] considered tentatively under the section on thrombophilia, satisfies most of the criteria set forth by Frøvig and probably represents the same

disease. Savory's case (p. 708) might conceivably fall into this group. Japanese authors [28] refer to 33 cases of this obscure type of arteritis in young persons; of these only three were men.

Other cases of this "young female" arteritis variety of the aortic arch syndrome are reported by Lewis and Stokes [7] and Giffin.[23a] These authors described a continuous murmur (with the acoustic characteristics of a patent ductus murmur) located above the sternoclavicular joint. Aggeler's patient [15] likewise had a continuous murmur above the left sternoclavicular joint. Oota [31] refers in some detail to 14 cases reported by Japanese authors. These 14 persons, with ages varying from 15 to 27 years, were with a single exception all female. At least one had cataracts. One was said to have had a patent ductus arteriosus; it seems very likely that what

Summary of Cases of the "Young Female" Arteritis Type of Aortic Arch Syndrome *

Author	Age, Yr.	Sex	B. P., Legs, Mm. Hg	Cataract	Atrophy, Face	Nasal Septum	Continuous Murmur	Vessel Involved: Right Subclavian	Right Carotid	Innominate	Left Carotid	Left Subclavian	Biopsy Findings
Harbitz [13]	36	F	.....	+	+	+	..	+	+	..	+	+	Arteritis
Marinesco [13c]	38	F	140/90	..	+	+	..	+	+	+	+	+	Atheromatosis ?
Oota [31]	25	F	146/100	+	..	..	..	+	+	..	+	+	Arteritis
Frøvig [3]	20	F	170-230 / 100-150	+	..	..	..	+	+	..	+	+	Arteritis
Maspetiol [12d]	23	F	100/40	..	+	+	..	+	+	±	+	+	Periarteritis nodosa ? (autopsy)
Takahasi [27b]	20	F	.....	+	..	..	..	+	+	..	+	+	.....
Lewis [7]	43	F	130-150 / ?	..	..	..	+	±	+	..	+	+	.....
Giffin [23a]	18	F	175-190 / 90-110	..	..	..	+	+	±	..	+	+	.....
Aggeler [15]	25	F	160-170 / ?	+	..	+	+	+	+	..	+	+	.....
Southworth [29a]	25	F	150/?	..	..	..	+	+	+	..	+	±	.....
Sato [30]	25	F	.....	+	..	..	..	+	+	..	+	+	Periarteritis or syphilis
Skipper [11]	37	F	150/90	+	..	..	+	+	+	..	+	+	Normal (nonthrombosed vessels)

*See Oota [31] for reference to 14 other less well-documented cases. Carcamise and Whitman [2b] review a large number of Japanese cases, of which 39 appear to fall into the "young female" group.

was heard was the continuous murmur described by others who have reported this syndrome. The Table summarizes these and other cases of this interesting syndrome. Not included is the case of a 53-year-old white man with involvement of all branches of the arch [16]; syphilis, periarteritis, and arteriosclerosis were apparently excluded and arteritis of some other form seemed likely.

Below is abstracted the clinical history of a patient who may fall into the "young female" group.

E. F. was admitted to the hospital at the age of 25, complaining of dizzy spells and fainting. She stated pulse and blood pressure had always been difficult to obtain in the arms. For a time after her first pregnancy, at age 22, she had had severe pain in the left side of her neck posteriorly, radiating to the occiput. During the labor of her second delivery, at age 25, she again had this pain in the neck. After delivery, under ether anesthesia, she is said to have gone into shock, in which state she remained five or six days, during which time unrevealing laparotomy for suspected ruptured uterus was performed. She was considered on discharge from

the hospital to be well, but three weeks after delivery she began to have pain in the right side of the neck and occiput identical to that on the left. About four weeks after delivery there was onset of dizziness and faintness with assumption of the upright position, with occasional brief periods of unconsciousness.

Examination revealed that in both carotid arteries and the right radial artery pulsations could not be felt; the left radial pulse was weak and inconsistent. Above the left clavicle a to-and-fro systolic-diastolic murmur was heard, loudest with the patient upright. This was audible below the clavicle as far as the pulmonic area but was faint there. Over the lower part of the left carotid a systolic thrill was palpable. Blood pressure could not be obtained in the right arm, was 120/90 in the left arm, and was 150 (systolic) by palpation in the legs, where pulses were normal. There were no definite abnormalities on chest x-ray except for possible dilatation of the pulmonary artery. Angiocardiograms likewise revealed this last finding together with several abnormal features in the aorta: Only one branch of the arch was visualized, and beyond it the aorta immediately narrowed so that the descending aorta was distinctly small. High on the descending aorta there was a slight outpouching which from its contour and location suggested the infundibulum of the ductus arteriosus. During cardiac catheterization ventricular fibrillation developed. Her dramatic recovery following 45 minutes of artificially maintained circulation is described elsewhere.[29a] Most recent information (February 1952) from the patient is that she is essentially asymptomatic.

Although this patient was at first thought to have patent ductus arteriosus with congenital atresia of some of the arch branches, the striking similarity to reported instances of the "young female" variety of aortic arch syndrome makes the latter diagnosis appear more tenable.

In another young woman (J. H. H. 541885), 27 years old, aching and easy fatiguing of the left arm developed after an acute illness of one month's duration, termed "rheumatic attack" by her and characterized by fever, polyarthritis, and myalgia. Two years later she was found to have no pulses and unobtainable blood pressure in the left arm. Aortograms showed occlusion of the left subclavian artery at its origin from the arch. Radio-opaque dye introduced retrograde into the left brachial artery passed back no farther than its junction with the axillary artery. Detailed studies revealed no cause for this vascular occlusion, but the nature of the illness that preceded the onset of symptoms suggests that some variety of arteritis may have been the cause.

In yet another recent case (607527), a 41-year-old white woman complained of attacks of shooting pain in the left side of the face accompanied by swelling of the left side of the neck. The left radial pulse was absent. Although the left carotid pulse appeared to be normal, it seems plausible that nonsyphilitic arteritis is the cause of this patient's symptoms.

The thrombosing arteritis responsible for this clinical syndrome in young women has been thought by Maspetiol and Taptas[124] to be a "disease of adaptation" as described by Selye. It has resemblances to, yet distinct differences from, periarteritis nodosa. Histologically the cases have shown giant-cell inflammation.[2a] No acid-fast bacilli have been identified. Positive tuberculin tests occurred in all of 12 cases tested, leucocytosis in 6 out of 10 cases, and rapid sedimentation in 18 out of 20 cases.

124. Maspetiol, and Taptas: Thrombosis of the Large Branches of the Aortic Arch in a Young Woman: Relationships to Multiple Thrombosing Arteritis, Semaine hôp. Paris **84**:2705, 1948.

Embolism.—It is well recognized that large emboli may be thrown off from aortic plaques or from the left ventricle or left atrium or their valves or may pass through an intercameral septal defect to the systemic circulation. It seems highly probable, though less well substantiated, that systemic emboli may arise in the pulmonary veins following pulmonary infarction, suppurative lung disease, and other pulmonary conditions associated with pulmonary phlebothrombosis. The following case appears to be an example of this last source for systemic emboli.

P. T. (J. H. H. 465364) was a white man who died at age 45. He had been of dissolute and sluggardly character most of his life and drank large amounts of alcoholic beverages quite steadily over a period of many years. Four months before death he suddenly "passed out" and on regaining consciousness he discovered he was paralyzed in all four extremities. He rapidly recovered use of his left arm and leg but right hemiplegia and aphasia persisted. He entered the hospital because of dyspnea and fever. By physical examination and x-ray he was found to have involvement of the right lung base. He died soon after admission. Serological tests for syphilis were negative.

Necropsy revealed findings which permitted the following reconstruction of events: There were septic organizing thrombi in the right iliac vein, right auricular appendage, and right ventricle, with multiple emboli to the lung, some of which had resulted in abscess formation. The left common carotid artery was completely occluded at its ostium by organized thrombus. The endothelium had largely covered the area so that only a dimple remained on the intimal surface. The aorta and its other main branches showed no unusual degree of atheromatosis and no evidence of syphilitic involvement. There was therefore reason to presume that the occlusion of the carotid was due to embolism. There was no discernible source of emboli in the left auricle or ventricle; the pulmonary veins were, in our opinion, the most likely source. The routine postmortem techniques are likely to overlook clots in this site.

In at least one of the cases of Penzoldt [92] embolism was probably the basis for occlusion of the right common carotid artery, which arose separately from the aorta as in arch Type 5 (see above). In Hutchinson's case,[125] discussed under neurogenic pulse changes, there may have been embolism of the left carotid artery similar to that occurring in the above patient (P. T.).

In Haffner's case [126] the emboli which occluded the left common carotid artery at its origin from the arch as well as the right brachial and left axillary arteries had their origin in the left atrium in a case of mitral stenosis. Högerstedt and Nemser [127] presented those cases in which they believed embolism to have been the basis for occlusion of great vessels at the aortic arch; this may have been true in some of the cases although in some syphilis seems to be a likely cause. The case of a weak pulse in the right common carotid reported by Smith and Hinshaw [20] occurred in a patient with chronic auricular fibrillation and may have represented embolism.

Extravascular Upper Mediastinal Tumor.—Pulse change due to nonvascular tumors of the upper mediastinum must be exceedingly uncommon. In a review of 200 miscellaneous types of mediastinal tumors at this hospital we could find no instances of pulse changes due to tumors other than aneurysm. That such should

125. Hutchinson, J.: Obliteration of the Left Carotid with Right Hemiplegia, Arch. Surg. **7**:36, 1896.

126. Haffner, S.: Obliteration of the Left Common Carotid and Both Brachial Arteries as a Result of Embolism in Heart Failure, Deutsches Arch. klin. Med. **60**:523, 1898.

127. Högerstedt, A., and Nemser, M.: Morbid Narrowing and Occlusion of the Great Vessels Arising from the Aortic Arch, Ztschr. klin. Med. **31**:130, 1897.

be the case is easy to understand if one recalls that by and large even in the case of aneurysms the pulse changes are a function, not of their space-occupying characteristics, but rather of associated aortitis or thrombus formation.

By this method for simultaneous recording of pulses from corresponding arteries of the two arms, Oda [37a] demonstrated minor degrees of pulsus differens in cases of mediastinal tumor. Although we have been unable to locate the original publication, Ehrmann is said by Pilz [55] to have observed pulse changes with substernal thyroid. Ekgren [128] described difference in blood pressure between the two arms in a case of "movable mediastinal tumor." The difference was more marked with the patient in the recumbent position.

ALLIED CONDITIONS IMPORTANT IN DIFFERENTIAL DIAGNOSIS OF THE AORTIC ARCH SYNDROME

Included in the aortic arch syndrome are only those cases in which the cause of the vascular obstruction is at or near the origin of the great vessels from the aortic arch. It is often difficult to ascertain the exact location of the lesion in the living patient. Consequently, many other causes of diminished or absent pulsation in the head or neck must be considered. Trauma to the great vessels in the neck or axilla may lead to thrombosis.[129] An unusual example of this was observed at this hospital in a 27-year-old baseball player (J. H. H. 391745) who noted undue tiredness in his right arm after pitching a game of baseball and was found to have thrombosis of the axillary artery. Thromboangiitis obliterans involves the distal vessel of the upper extremity as well as the lower, resulting in absent pulsation. Severe arteriosclerosis of the peripheral vessels may render the pulses impalpable. Aortic stenosis is occasionally so extreme as to render the patient pulseless. Anomalous arterial patterns in the arms must be considered when peripheral pulses appear to be feeble or absent.

Thoracic Outlet Syndrome.—The thoracic outlet syndrome with or without cervical rib must be considered in the differential diagnosis of the aortic arch syndrome. This subject has been adequately reviewed by Eden [130] and more recently by Beyer and Wright.[131] In these cases the arterial wall may be damaged at the point of compression in the thoracic outlet. Aneurysmal dilatation often develops distal to the constriction. Thrombosis of the vessel may occur, with peripheral extension or peripheral embolization. Absence of pulse in the involved arm does not, however, necessarily indicate thrombosis. In this group of cases pain and trophic changes in the arm are much more prominent than in the case of occlusion at the arch. In Eden's review [130] of 45 cases no retrograde extension of thrombosis to the aorta was recorded.

The following case, though complicated in many respects, illustrates many of the problems encountered in dealing with thoracic outlet cases.

128. Ekgren, E.: An Unusual Blood Pressure Finding in a Case of Mediastinal Tumor, Fortschr. Med. **20**:105, 1902.

129. Hunt.[9d] Footnote 84*a* and *c*.

130. Eden, K. C.: Vascular Complications of Cervical Rib, Brit. J. Surg. **27**:111, 1939.

131. Beyer, J. A., and Wright, I. S.: The Hyperabduction Syndrome: With Special Reference to Its Relationship to Reynaud's Syndrome, Circulation **4**:161, 1951.

T. T. F. (J. H. H. 201113), a 67-year-old retired white carpenter, was admitted May 17, 1940, complaining of weakness, numbness, and coldness of the left hand, which had developed gradually during the 10 years prior to admission. During the five years before admission he had suffered from frequent infections of the left hand, necessitating amputation of one finger. The radial pulse was much stronger in the right arm. The left arm was colder than the right. There was a palpable mass in the left supraclavicular fossa. The serological test for syphilis was repeatedly positive in low titer. At operation a subclavicular lipoma was removed, a taut scalenus anticus muscle divided, and the axillary artery explored. The axillary artery had no visible pulsation before or after division of the scalenus muscle. No cervical rib was discovered. Postoperative blood pressures were 175/80 (right arm) and 105/70 (left arm).

The patient was readmitted two years later (Nov. 25, 1942) because of frequent finger infections on the left hand. Blood pressure was 170/90 mm. Hg in the right arm and 120/90 mm. Hg in the left. The terminal phalanges of the left fourth and fifth fingers were blue and cold, and the left second finger was gangrenous. The left carotid, subclavian, brachial, axillary, and radial pulses were barely palpable and were much weaker than on the right. Laboratory examination revealed a positive serological test for syphilis. Other routine studies were normal. X-ray of the chest showed the heart to be slightly enlarged, and the aorta slightly dilated and tortuous. No cervical rib was seen.

The left neck was explored a second time and no pulsation could be felt in the left subclavian or axillary arteries. The left carotid was described as having "scarcely perceptible pulsation." The operator palpated the subclavian and innominate arteries behind the sternoclavicular joint and felt no pulsation. Four days later a left dorsal sympathectomy was performed, and the patient was discharged essentially unchanged Dec. 29, 1942.

It was later learned that right hemiplegia developed, and the patient died on March 7, 1943. Autopsy was not performed.

In retrospect it seems possible that this case was one of syphilitic aortitis without aneurysm, with narrowing of the ostia of the left carotid and subclavian arteries. The hemiplegia may have represented thrombosis or complete occlusion of the left carotid artery. Compression at the thoracic outlet, with irreversable changes in the vessels of the extremity and retrograde thrombosis to the aortic arch, must also be seriously considered. Symonds[1] described two somewhat similar cases, in which a right cervical rib apparently precipitated a thrombotic process in the subclavian artery, when extended in a retrograde fashion to the innominate artery, where emboli were liberated into the carotid artery. The symptoms referable to inadequate circulation in the left arm are, as previously mentioned, more in keeping with the thoracic outlet syndrome than with syphilitic aortitis and occlusion. It is possible that this represents a combination of two diseases.

Neurogenic Pulse Changes.—Occasionally one may observe marked reduction in the pulses in the arm and leg involved by hemiplegia secondary to cerebrovascular accident (according to Oda,[37a] differences in the radial pulse following hemiplegia were first observed by Torain in 1870). In rare instances complete obliteration of pulses may occur, as described below. This vasomotor phenomenon is most often the result of damage to the premotor frontal cortex and can be reproduced in animals by appropriate ablation,[132] and in man by stimulation of the cerebral cortex.[133]

132. Kennard, M. A.; Viets, H. R., and Fulton, J. F.: The Syndrome of the Premotor Cortex in Man: Impairment of Skilled Movements; Forced Grasping and Vasomotor Disturbance, Brain **57**:69, 1934.

133. Bucy, P. G.: Vasomotor Changes Associated with Paralysis of Cerebral Origin, Arch. Neurol. & Psychiat. **33**:30, 1935.

Lesions in the thalamus have been observed to produce this phenomenon.[84b] The lesion in man may be vascular in type [133] or, less commonly, tumor [134]; one instance due to carbon monoxide poisoning has been reported.[135] The vascular phenomenon may be greatly out of proportion to motor weakness. The pulse alteration may be transitory [133a] or may persist over a period of many years.[136] The vasoconstriction may lead to gangrene of the foot [137] on the affected side. Van Balen [138] described several cases of anisosphygmia due to cerebral vascular accidents and observed that the blood pressure was usually higher in the involved arm immediately after the occlusion, falling to a level below that in the normal arm in cases in which the vascular accident was remote. He suggested that this observation might be more apparent than real, being due largely to spasticity and flaccidity of the arterial wall musculature and surrounding structures. Results of investigation of this problem using modern techniques for studying the peripheral circulation would be of interest.

Hutchinson's case [125] of decreased pulses in hemiplegic limbs, though not recognized at the time, is cited as an example of neurogenic pulse change. This patient, a fox-hunter of 46 years, was found unconscious one morning on the hearth rug. He was for a time aphasic with a right hemiplegia but recovered except for residual weakness of the right arm and leg. When examined by the author four years after the "fit," the pulses in the left common carotid, right femoral, and right brachial arteries were absent. Hutchinson postulated that the hemiplegia was secondary to sudden occlusion of the left common carotid artery and made the following sage comment:

> Such cases as this suggest that it might be of interest and advantage to examine the arterial system more often and more systematically than is usually done. This patient had been attended after his fit by a distinguished specialist, but unfortunately the finger had never been put on his carotid, or the cause of the hemiplegia would have been at once obvious.

As to the etiology of the carotid obstruction Hutchinson makes no comment, but he did note that the patient had evidence of iliac vein obstruction on the right, with dilated and tortuous epigastric veins. It is possible that an embolus originating in these veins passed to the carotid artery through a patent foramen ovale or initiated a pulmonary venous thrombosis similar to that postulated in the case of P. T. (p. *732*). It seems most likely that the decrease in pulse in the right arm and leg was secondary to hemiplegia. An alternate explanation for the carotid occlusion is syphilitic aortitis, since Hutchinson believed the patient had had syphilis previously.

133a. Penfield, W.: The Evidence for a Cerebral Vascular Mechanism in Epilepsy, Ann. Int. Med. **7**:303, 1933-1934.

134. De Morsier, G.: Sympathetic Hemisyndrome with Absence of Radial and Pedal Pulse: Thalamic Tumor, Rev. méd. Suisse Rom. **60**:1026, 1940. Zenner, P., and Kramer, S. P.: Operation for Brain Tumor with Occurrence of Hitherto Unrecognized Circulatory Phenomena, New York M. J. **90**:651, 1909.

135. Popper, L.: Cerebrally Determined Pulsus Differens, Med. Klin. **27**:1275, 1931.

136. (*a*) Kerr, W. J., and Underwood, F. J.: Hemiconstruction of the Vascular System Associated with Cerebral Disease, Am. Heart J. **12**:713, 1936. (*b*) Melchior, E., and Wilimowski, M.: Suppression of Pulses in Paralyzed Limbs, Zentralbl. Clin. **43**:49, 1916.

137. Kerr, W. J.: Personal communication to the authors.

138. Van Balen, G. F.: Changes in the Pulse and Blood Pressure After Cerebro-Vascular Accidents, Nederl. tijdschr. geneesk. **73**:5861, 1929.

The case reported by Kerr and Underwood[136a] is exceedingly interesting. Right hemiplegia with aphasia developed at the age of 23 years in this white man. The nature of the presumed left cerebral hemisphere lesion was never elucidated. Speech returned, but there was onset of epileptic seizures. From the age of 33 until the present (age 51) the patient has been under the observation of Dr. Kerr. Throughout this period pulsation has been greatly reduced or absent in all arteries on the right side of the body. There has been persistent severe hypertension on the left. In this connection it is interesting to note that intravenous pyelograms revealed a small right kidney as compared with the left. Studies to demonstrate a spastic element in this man's condition failed, and it has been assumed that structural changes have occurred secondary to the prolonged spastic constriction of the arteries on the right side. The patient is still living (December, 1951); amputation of the right leg for gangrene has been necessary.[137] Another patient in whom marked anisosphygmia followed a cerebral vascular accident was reported by Pilcher and co-workers.[139]

At this hospital two patients with superannuated hemiplegia and neurogenic pulse changes have come to our attention.

One man (J. H. H. 211339), who had suffered a right-sided paralysis at the age of 36 years, was found 13 years later to have minimal residual stiffness and weakness in the right arm and leg; the right arm pulses were very weak, with blood pressures of 65/58 (right arm) and 130/75 (left arm).

A second patient (J. H. H. 130600) had severe hypertension which was believed to be the result of periarteritis because of the presence of eosinophilia, leucocytosis, and otherwise unexplained recurrent abdominal pain. The patient was observed over a period of four years. During that time a cerebrovascular accident with left hemiplegia occurred. Thereafter it was observed repeatedly that pulse and blood pressure could not be detected in the left arm.

Embolus Remote From the Aortic Arch.—Embolism to main arteries of the upper extremities should not be confused with any form of the aortic arch syndrome. A history of abrupt onset of pain in the embolized extremity should be obtainable and the patient is likely to have evidence of circulatory embarrassment in the arm, symptoms which are notably absent in the aortic arch syndrome. When there is a plausible central source for the emboli, such as a fibrillating left auricle or myocardial infarct, the diagnosis is practically certain.

In two instructive cases at this hospital pulse changes which were interpreted as due to changes in the aorta were demonstrated to have resulted from embolism.

A 54-year-old white woman (J. H. H. 135074) was admitted in congestive heart failure due, it seemed, to hypertension. Pulse and blood pressure were unobtainable in the left arm. Autopsy revealed an organized and recanalized thrombus in the proximal portion of the left brachial artery. There was a healed myocardial infarct of the apex of the left ventricle, with an organizing mural thrombus and evidence of embolism of small coronary artery branches. An episode two years before death had the characteristics of acute infarction, yet at the time of the terminal admission six sets of electrocardiograms (with only one chest lead) showed no definite evidence of the myocardial infarct. It is significant that one observer had reported that a "slight pulsation" was palpable high in the left axilla.

Ten days after an operation on the lumbar spine the other patient (J. H. H. 402371), a 64-year-old Negro man, had excruciating abdominal pain, pulselessness and pain in the left arm,

139. Pilcher, C.; Wyatt, T. E., and Carney, H. M.: Infarction of the Brain with Unilateral Circulatory Changes, Arch. Neurol. & Psychiat. **45**:321, 1941.

and hematuria followed by oliguria. Blood pressure was unobtainable in the left arm, but pulses could be felt in the left subclavian and axillary arteries. The left femoral pulse was weak. The most likely diagnosis was considered to be dissecting aneurysm of the aorta with dissection of the left arm arteries and occlusion at a distance from the arch by the mechanism described earlier. The patient had varicose veins of the legs, with hard palpable thrombi, and the existence of paradoxical emboli was considered but thought less likely than dissecting aneurysm. Autopsy revealed infarction of the bowel supplied by the superior mesenteric artery; multiple pulmonary emboli, and emboli to the coronary, left brachial, and left femoral arteries. The foramen ovale was open partly as the result of distention of the right auricle. In retrospect all the circumstances of the case pointed to the correct diagnosis of paradoxical embolism from the leg veins. In such cases weight should be placed on the signs of pulmonary emboli, since the elevation of pulmonary artery pressure so produced is a leading factor responsible for passage of emboli through the foramen ovale.

DIAGNOSTIC WORK-UP

The diagnostic evaluation of patients with the aortic arch syndrome is worthy of special consideration. The history should be taken with particular attention to possible history of syphilis, chest trauma, heart disease, chest pain, and symptoms of arterial insufficiency. The physical examination should include a complete examination of the pulse. By this we mean careful palpation for the pulse at several levels in the involved limb to determine, if possible, the level of the occlusion. Anomalous distribution of vessels in the extremity should be excluded by the examination. The pulse should also be felt during the usual maneuvers designed to detect thoracic outlet compression. The blood pressure should be determined in the arms and legs. The Gaertner method, described previously, may be useful in this regard. In addition to auscultation of the heart, the examiner should direct his attention to the supraclavicular fossae, the axillae, and the neck. An expert examination of the eyes and nose should be made for trophic changes so commonly seen in these organs when the carotid circulation is impaired. In addition to the routine serological tests for syphilis, the treponemal immobilization test [12c] should be performed to detect seronegative syphilis. Blood coagulation studies and a platelet count are indicated by the suggestion that thrombocytosis may play a role in some cases. The serum cholestrol level should be determined to detect hypercholesterolemia, a potentially treatable condition.

Chest x-ray and fluoroscopy may reveal diagnostic changes in the aorta or great vessels. Aortograms are often necessary to localize the occlusive disease. The opaque medium may be injected into the aorta through one of the branches of the arch or it may be introduced via a catheter passed in a retrograde fashion from the femoral artery into the aortic arch. This procedure is usually more satisfactory than angiocardiography, as a larger concentration of dye can be introduced into the aorta. Retrograde injection of the pulseless vessel with opaque medium is useful in determining the peripheral extent of the occlusive process. Biopsy of skin, muscle, and lymph nodes may give useful information if the occlusions are secondary to some generalized disease. The most direct procedure is that of biopsy of the involved artery, when it is completely occluded. Unfortunately, microscopic examination of the involved artery is not always helpful, as the removed segment often shows only thrombus and secondary changes in the vessel wall.

TREATMENT

Treatment should quite naturally be directed at the etiological process, when possible. Antisyphilitic therapy has restored pulses in three cases of syphilitic aortitis.[140] Although the pulse abnormality of dissecting aneurysm was frequently observed to disappear when the intramural hematoma was absorbed and although it is believed that the progress of atheromatosis was stayed by a low-fat diet in a few patients, no patient in this study other than those with syphilitic aortitis showed reversibility of their disease. The improvement in the syphilitic patients would suggest the presence of significant edema as a factor in the occluding process. Relief of angina by treatment of patients with syphilitic aortitis and involvement of the coronary ostia is a familiar and analogous situation.[141] If the process is medically irreversible, surgical therapy may be possible. Dr. Gordon Murray,[142] of Toronto, operated on one of the patients (A. L. Case 6, p. 714) reported in this series. This patient had syphilitic aortitis with obliteration of all four great vessels. The left common carotid artery was opened and was found to have a patent though contracted lumen. A probe was passed down through the vessel until firm resistance was encountered at the place where the vessel arose from the aorta. The probe was passed into the aortic lumen, and a free flow of blood returned into the carotid. The opening was enlarged by further instrumentation until a very good pulsatile flow came into the carotid. The carotid artery was closed and good pulsation was felt in the vessel above the operative site. It seems likely that similar operations might be employed in other patients in whom the vascular lumen is open distal to the obstruction. In essence, this procedure is a thromboendarterectomy, which has been practiced with success in other areas of the body, including the bifurcation of the common carotid artery.[28a] Dr. Murray suggested another alternative procedure, applicable for those patients in whom the subclavian arteries are not occluded. A functioning subclavian artery could be anastomosed to a patent but bloodless carotid artery distal to the obstruction. These procedures, directed at restoration of the carotid circulation, are certainly worth while, as most of the symptoms and irreversible changes are in the head.

In the treatment of thrombosis of the internal carotid artery procedures that have been tried include removal of a segment of the involved artery, periarterial sympathectomy, and cervical ganglion sympathectomy.[143] The results have not been impressive. From the experience of Roseman and co-workers [21] there is reason to believe that excision of the carotid bifurcation might be curative of the symptoms due to sensitive carotid sinus in combination with the aortic arch syndrome.

In view of the rapid advances which are continually being made in vascular surgery it seems entirely within the realm of possibility that reconstructive surgery of the aortic arch will become possible. Grafting of the bifurcation of the aorta

140. Lampen and Wadulla.[28b] Nygaard and Brown.[117] Case of E. M., presented in this paper.

141. Edeiken, J.; Ford, W. T., and Stokes, J. H.: Observations in Penicillin Treated Cardiovascular Syphilis, Pennsylvania M. J. **54**:229, 1951.

142. Murray, G.: Personal communication to the authors.

143. Reichert, T.: Arteriography of the Cerebral Vessels in Unilateral Occlusion of the Internal Carotid, Nervenarzt **11**:290, 1938. Wolfe, H. R. I.: Unexplained Thrombosis of the Internal Carotid Artery, Lancet **2**:567, 1948.

has already been successfully performed by Oudot [144] and others in Leriche's syndrome of thrombotic occlusion at that site. Replacement of the entire aortic arch in dogs by means of homologous grafts is under active study.[145]

In one of our patients with probable complete occlusion of all the major branches of the aortic arch by syphilitic aortitis, Dr. Henry T. Bahnson has recently grafted a lyophilized infant's aorta between the arch and the patent portion of the common carotid artery. The patient's dizziness, tinnitus, and convulsions have been relieved, although the period of follow-up is too short for complete evaluation of results.

Atherosclerosis is probably not amenable to therapy in the late stages. If associated with hypercholesterolemia, a low-fat low-cholesterol diet is indicated.[146] There is promise that other methods of slowing the advance of atheromatosis will be developed in the near future. At present little more than supportive care can be suggested for the chronic dissected aorta. The treatment of arteritis is difficult, in that the etiology remains obscure.

SUMMARY AND CONCLUSIONS

Clinicians have long been perplexed by occasional instances of the aortic arch syndrome, i.e., cases with obstruction of the great vessels at or near their origin from the aortic arch. An attempt has been made to assemble an etiological classification which would assist in diagnosis and treatment of the individual case.

The classification and discussion presented here are based on a review of over 100 cases, of which 35 are previously unreported.

Syphilitic aortitis is undoubtedly the most common cause of this syndrome. The presence of aneurysm is by no means essential. In fact, saccular aneurysm was present in less than half of the cases with great vessel obstruction due to syphilis of the aorta. In all cases of syphilitic origin, with and without aneurysm, intimal proliferation and cicatrization represent by far the most common mechanisms of obstruction. In only 3 of 44 cases, for instance, was antemortem thrombus (a phenomenon seen only in saccular aneurysm) responsible for the occlusion. Secondary atheromatosis of the syphilitic aorta is undoubtedly an important contributing factor in great vessel obstruction.

Atheromatosis is surprisingly uncommon as a primary cause but may contribute in the traumatic and congenital cases, as it almost certainly does in those of syphilitic aortitis.

We have suggestive evidence that trauma of certain special types may lead to occlusion of the large arch branches, perhaps after a considerable delay. The factor of trauma is worthy of further consideration in the future.

Of the five main varieties of aortic arch branching, the less common patterns were encountered at autopsy with unexpected frequency in cases of the aortic arch syndrome. Congenital types of pulse abnormalities in the upper part of the body are reviewed.

144. Oudot, J.: Graft of the Aortic Bifurcation from the Renal Arteries to the External Iliac Arteries for Arterial Thrombosis, Mém. Acad. chir. **77**:642, 1951.

145. Hardin, C. A., and Schafer, P. W.: Total Replacement of the Aortic Arch by Means of Homologous Artery Grafts and Mechanical Shunts, read before the Society of University Surgeons, Baltimore, Feb. 8, 1952.

146. Hildreth, E. A.; Hildreth, D. M., and Mellinkoff, S. M.: Principles of a Low Fat Diet, Circulation **4**:899, 1951.

Attention is drawn to the unsolved and confused problem of arteritis of the larger vessels. In most cases of involvement of the aorta and its large arch branches, it is uncertain whether the process represents Buerger's disease, periarteritis nodosa, "giant cell arteritis," or some other disorder.

The clinical manifestations result almost exclusively from the impediment to carotid artery blood flow (interference with vertebral blood flow by obstruction of the subclavian arteries is doubtless an additional factor of importance in some cases). Whereas cerebral, eye, ear, and face changes are outstanding features of the clinical picture in some cases, symptoms referable to the arms are conspicuous by their absence.

Therapy can be directed at the etiological factor, in the case of syphilis at least, and striking benefit has been observed in two patients. Surgical approaches to the treatment of all varieties of the aortic arch syndrome should be explored further.

Case Reports

SARCOID AND SARCOID-LIKE GRANULOMAS OF THE STOMACH

A Clinical Evaluation

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THE STOMACH is not often cited as the location of sarcoid and sarcoid-like granulomas, nor can a specific clinical syndrome be attributed to involvement of the gastric mucosa by such lesions. Symptoms and clinical findings, occasionally of serious import, have been reported, however, in association with the finding of noncaseating granulomatous lesions in the stomach. The subject, therefore, seems worthy of review.

The histologic diagnosis of sarcoid is sometimes difficult, even with carefully prepared biopsy material. Engle,[1] in an article concerned chiefly with the pathology of these granulomas, found the stomach to be involved in 3 of the 27 autopsies he reviewed. One of the patients was a 54-year-old white man who died of hemorrhage from a duodenal ulcer after a protracted illness characterized by a gradual downhill course. Sarcoid-like granulomas were found in the gastric mucosa, and these were later proved to be due to Histoplasma capsulatum. Because of the active peptic ulceration, it was difficult to determine the role of these foci in the production of the patient's symptoms of nausea, vomiting, epigastric distress, and hemorrhage. Another of his cases was of a 27-year-old white man who died of "undiagnosed generalized granuloma." The tuberculin skin test was negative; the serum proteins were normal. Caseation was noted in some of the granulomatous foci found elsewhere in the body but not in those involving the gastric mucosa. Acid-fast organisms could not be demonstrated in either of these cases, but Engle's third patient died of pulmonary tuberculosis. Necrosis was demonstrated in all of the lesions found elsewhere in this patient, but those in the gastric mucosa were singularly free of such abnormality. The serum proteins were normal. In none of these cases were there any gastrointestinal symptoms which could directly be attributed to the invasion of the gastric mucosa by the sarcoid-like granulomatous lesions.

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1. Engle, R. L.: Sarcoid and Sarcoid-Like Granulomas: A Study of 27 Postmortem Examinations, Am. J. Path. **29**:53-71, 1953.

Schaumann,[2] at an autopsy in 1936, made the incidental observation of epithelioid foci without necrosis in the mucosa of an atrophic thin-walled stomach. The patient had complained only of vague abdominal pain and had had widely disseminated sarcoidosis. Tuberculous peritonitis was demonstrated bacteriologically after death, which casts some doubt on the exact nature of the gastric lesions. Mesenteric lymph nodes showed typical caseous tuberculosis, but the lesions in the gastric mucosa were without necrosis.

Also in 1936 Naumann[3] reported the case of a 3-month-old infant who died of generalized sarcoidosis. Autopsy revealed "nodules in the stomach wall" which upon examination of microscopic sections were believed to be sarcoid. No gastrointestinal symptoms were recorded. The tuberculin skin test and Wassermann reaction were negative.

In the case reported by Kulka[4] in 1950, of a 26-year-old woman who died suddenly of what appeared to be sarcoid involvement of the heart, lesions interpreted as sarcoid were noted in the gastric mucosa. No symptoms referable to the gastrointestinal tract were mentioned.

Jessing[5] in 1943 reported the case of a 61-year-old white woman subjected to gastrectomy because of gastric ulcer. Lesions reported as sarcoid were discovered in the mucosa and submucosa of the resected organ. The ulcer was benign. Sarcoid foci were found nowhere else in the patient, and she was free of tuberculosis. Subsequently, Oppenheim and Pollack,[6] Longcope and Freiman,[7] and Guibert[8] each reported similar cases in which the stomachs of their patients, removed because of gastric ulcer, were found to contain lesions interpreted as sarcoid.

Gore and McCarthy[9] in 1944 reported the case of a 26-year-old soldier operated upon because of pyloric stenosis. Peptic ulcer, neoplasm, and gastric syphilis were all considered preoperatively as possible diagnoses. Serological tests were positive but had become so after the onset of gastrointestinal symptoms. The gastric juice contained no free hydrochloric acid following histamine stimulation. Microscopic section of the resected organ revealed foci thought to be typical of sarcoid. The granulomatous lesions had accumulated at the gastric outlet so densely as to interfere with its function. Some fibrosis, not an uncommon late addition to the sarcoid lesion, was noted in the muscularis propria. A superficial benign ulcer was noted in the region of the pylorus but was considered to be without significance in the production of the stenosis. Acid-fast organisms could be demonstrated nowhere

2. Schaumann, J.: Lymphogranulomatosis Benigna in the Light of Prolonged Clinical Observations and Autopsy Findings, Brit. J. Dermat. **48**:399-446, 1936.

3. Naumann, O.: Kasuistischer Beitrag zur Kenntnis der Schaumannschen "Benignen Granulomatose" (Morbus Besnier-Boeck-Schaumann), Ztschr. Kinderh. **60**:1-8, 1938.

4. Kulka, W. E.: Sarcoidosis of the Heart: A Cause of Sudden and Unexpected Death, Circulation **1**:772-776, 1950.

5. Jessing, A.: Lymforgranulomatosis benigna i ventriklen, Nord med. **17**:161-162, 1943.

6. Oppenheim, A., and Pollack, R. S.: Boeck's Sarcoid (Sarcoidosis), Am. J. Roentgenol. **57**:28-35, 1947.

7. Longcope, W. T., and Freiman, D. G.: A Study of Sarcoidosis, Med. Baltimore **31**:1-132, 1952.

8. Guibert, H. L.: Maladie de Besnier-Boeck-Schaumann á localization gastro-ganglionnaire pure (étude histo-pathologique), Ann. d'anat. path. **17**:295, 1947.

9. Gore, I., and McCarthy, A. M.: Boeck's Sarcoid: Report of a Case Involving the Stomach, Surgery **16**:865-873, 1944.

in the sections; the patient's tuberculin skin test was negative. The authors recalled one other case similar to theirs, presented by Dr. Fred Stewart at a conference of the New York Laboratory Association but never reported in the literature.

In the same year, Orie, van Rijssel, and van der Zwaag [10] reported an almost identical lesion in a 53-year-old white woman. The tuberculin skin test was negative, and the gastric analysis showed absence of free hydrochloric acid. Gastroscopy revealed a mucous membrane which appeared thickened and glassy. The antrum was rigid, no contractions could be seen, and the opening into the duodenum was small. They mentioned a surgical specimen found in the pathology museum of their hospital which must have been responsible for a nearly parallel clinical course. Unfortunately no details were available.

Appell, Pritzker, and Klotz [11] later documented a fifth case of pyloric stenosis presumably due to sarcoid. Their patient was a 48-year-old woman without evidence of sarcoid elsewhere. Free hydrochloric acid could not be demonstrated in the gastric secretions. There was no evidence of infection with acid-fast organisms.

The case of Moran's [12] patient, subjected to laparotomy because of possible gastric neoplasm, must be viewed with suspicion. Although the condition was reported as sarcoid of the stomach, no biopsy of the stomach itself was made, because exploration had revealed only generalized mural thickening and inflammation. Neighboring lymph nodes were found to contain granulomatous foci interpreted as sarcoid, and it was assumed that the stomach also contained such lesions.

Bauer [13] in 1951 reported the case of a 59-year-old woman for whom the preoperative impression of gastric carcinoma was confirmed upon microscopic study of the resected organ. However, granulomatous lesions interpreted as sarcoid were found among the neoplastic cells and also in areas of gastric mucosa free of malignant tissue. There was achlorhydria. The tuberculin skin test was negative, and the serologic test for syphilis was negative. Symptoms were those of the gastric neoplasm—nausea, epigastric pain, excessive gas, and severe weight loss.

Recently, McKusick [14] reported two patients presenting still different clinical manifestations of sarcoid or sarcoid-like granulomas of the gastric mucosa. The first, a 48-year-old woman, had complained of anorexia, vomiting, and weight loss. X-ray examination of the stomach suggested linitis plastica. The other, a 41-year-old woman, had had recurring episodes of gastrointestinal hemorrhage of undetermined origin. Gastrectomy was carried out in both cases, and microscopic examination of the resected specimens revealed mucosal lesions interpreted as sarcoid. Superficial mucosal ulcerations were noted in both. Tuberculosis could be demonstrated in neither, and the tuberculin skin tests were negative. With the exception of a few perigastric nodes in the first patient, there was no evidence of sarcoid elsewhere.

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10. Orie, N. G. M.; van Rijssel, T. G. and van der Zwaag, G. L.: Pyloric Stenosis in Sarcoidosis, Acta med. scandinav. **138**:139-143, 1950.

11. Appell, A. A.; Pritzker, H. G., and Klotz, P. G.: Pyloric Obstruction Due to Sarcoid of the Stomach, A. M. A. Arch. Surg. **62**:140-144, 1951.

12. Moran, J. G.: Enfermedad de Besnier-Bloeck-Schaumann con localizacion gastrica, Rev. clín. españ. **38**:187-190, 1948.

13. Bauer, J. T.: Granuloma (Sarcoid) of the Stomach (Report of Case Associated with Carcinoma), Bull., Ayer Clin. Lab. **4**:35-43, 1951.

14. McKusick, V. A.: Boeck's Sarcoid of the Stomach with Comments on the Etiology of Regional Enteritis, Gastroenterology **23**:103-113, 1953.

Interest in this subject was stimulated by two patients recently studied at this hospital. Altogether, gastric biopsies, using the vacum tube technique,[15] have been taken from 17 patients in whom sarcoid foci had been demonstrated in other organs. In only one of these (Case 1) were the granulomatous foci found. The vacum tube technique failed to demonstrate such lesions in Case 2, in which the diagnosis was made on a biopsy specimen taken during surgical exploration and had been unsuspected prior to operation.

REPORT OF CASES

CASE 1.—A 20-year-old Negro airman was born and lived most of his life in an urban area of northeastern United States. He had had no known contact with tuberculosis. In January 1951, following an episode of apparently simple conjunctivitis treated with penicillin locally, there was onset of progressive painless enlargement of the lacrimal glands of both upper eyelids. In addition the patient complained of malaise, slight decrease of visual acuity, and loss of about 20 lb. (9 kg.). A biopsy of the lacrimal glands revealed epithelioid foci interpreted as being "compatible with Boeck's sarcoid." The patient was therefore transferred to this hospital for further evaluation and treatment, in November 1951. At some time during this period there was onset of vague intermittent generalized abdominal discomfort and tenderness. This assumed no fixed pattern. There was no nausea, vomiting, or change in bowel habits.

Physical examination revealed no significant abnormalities other than a slight abdominal tenderness and obviously enlarged, slightly ptotic upper eyelids, which on palpation had a nodular consistency. Complete blood count, urinalysis, sedimentation rate, and chest x-ray were normal. The serologic studies showed no abnormalities. The serum calcium was 10.3 mg. per 100 ml., inorganic phosphorus 4.1 and 3.1 mg. per 100 ml., and alkaline phosphatase 6.6 and 2.7 units. Several estimations of the total protein and of the albumin : globulin ratio were carried out, and all were within normal limits. Electrophoretic study of the serum proteins revealed no hyperglobulinemia. A gastric analysis showed low total acid and only 4 units of free hydrochloric acid in one specimen following histamine stimulation. Numerous gastric washings were negative for acid-fast bacilli on culture. A gastrointestinal x-ray series was made, and, because of reported mucosal changes suggestive of polyposis, a gastroscopy was performed. In this examination the mucosa appeared grossly normal, but a biopsy of the gastric mucosa taken by the vacuum tube method revealed many foci of noncaseating granulomatous lesions (Figs. 1 and 2). These contained epithelioid and giant cells of the foreign-body type, which were surrounded by fibrous tissue containing numerous lymphocytes and plasma cells. X-ray survey of the skeleton revealed no bone lesions.

Hospital Course.—A tuberculin skin test, first strength, was positive. The patient continued to complain of vague abdominal discomfort, and at the same time the lacrimal glands of the upper eyelids continued to enlarge. On the basis of the histologic picture sarcoid was considered the most likely diagnosis, despite the paucity of other manifestations of the disease. Because of the danger of uveal tract involvement, treatment was begun with calciferol. Before the proposed course of therapy could be completed, however, toxic symptoms developed, chiefly of the gastrointestinal system, necessitating discontinuance of that drug. No benefit could be noted from its use.

The patient was therefore treated with corticotropin (ACTH), receiving a total 165 mg. intravenously over a 10-day period. Because of the positive tuberculin reaction, the unsavory reputation of corticotropin with regard to tuberculosis,[16] and the unsettled role of tuberculosis in the etiology of sarcoid, the patient was given streptomycin and *p*-aminosalicylic acid concurrently with and for two weeks after treatment with corticotropin. Satisfactory adrenotrophic response was reflected in a sharp fall in the circulating eosinophiles. Following this course of therapy there was slight softening and decrease in the size of the lacrimal glands. Rebiopsy of the stomach mucosa, however, revealed no change in the previously described granulomatous

15. Palmer, E. D.: Correlated Gastric Mucosal Biopsy Findings and Gastroscopic Diagnoses: Preliminary Report Based on 50 Patients, Am. J. M. Sc. **219**:648-650, 1950.

16. Cortisone, Corticotropin and Tuberculosis, Editorials and Comments, J. A. M. A. **149**: 1474, 1952.

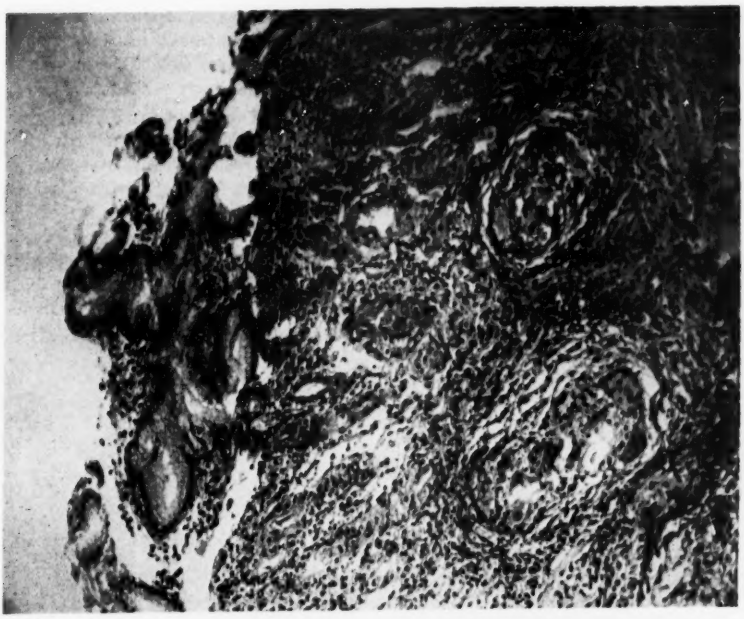

Fig. 1 (Case 1).—Section of gastric mucosa, showing scattered granulomatous foci; × 110.

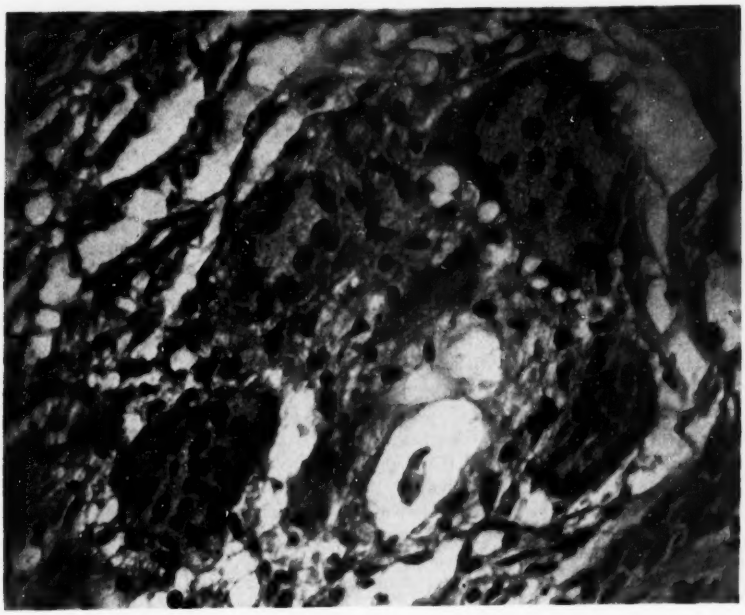

Fig. 2 (Case 1).—High power magnification of a part of Figure 1, showing detail of the giant cells; × 660.

lesions. The patient was returned to duty. When he was examined 10 months later, there was no further enlargement of the lacrimal glands nor was there change in the histologic appearance of the gastric mucosal lesions. The tuberculin skin tests were repeated and had become negative in the second strength. The gastrointestinal symptoms were unchanged.

CASE 2.—A 25-year-old white soldier had served in the South Pacific and Europe during his seven years of military service. He had had no known contact with tuberculosis, nor had he had any significant illnesses in the past. He was well until October 1951, when there was onset of gradually progressive anorexia, weakness, and bloody diarrhea, followed by left upper quadrant pain, nausea, and vomiting. There were several episodes of hematemesis. Upon admission to the local hospital, examination was negative save for slight left upper quadrant tenderness and anemia. Gastrointestinal studies and barium enema showed no abnormalities. Treatment with bland diet and iron brought about relief of the patient's symptoms and correction of the anemia.

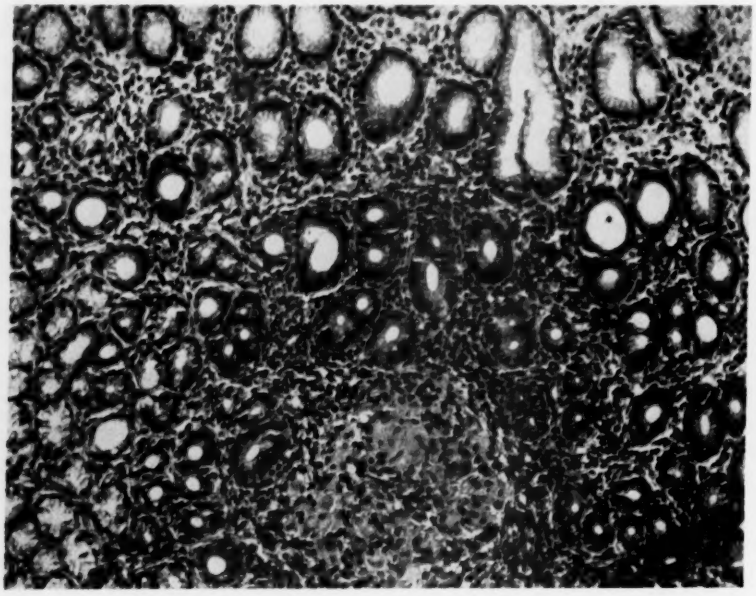

Fig. 3 (Case 2).—Low power view of gastric mucosa, showing single granulomatous focus; × 110.

He was returned to duty. He felt well until October 1952, when his symptoms recurred more severely than before. He was hospitalized once again and treated with bland diet, antacids, antispasmodics, and transfusions of whole blood. Repeat gastrointestinal x-ray series and barium enema showed no abnormalities. Proctoscopy also showed no abnormalities. Gastroscopic examination showed the stomach to be full of blood, with clots adherent to the mucosa.

The patient was transferred to this hospital for further study, with a diagnosis of hemorrhagic gastritis, cause undetermined. His complaints of weakness and left upper quadrant tenderness persisted. He had lost approximately 15 lb. (6.7 kg.). Physical examination was not remarkable except for slight pallor and left upper quadrant tenderness. Results of chest x-ray, urinalysis, white blood cell count, differential cell count, and serologic test for syphilis were normal. The red blood cell count was 4,050,000; hemoglobin, 76% (11.9 gm.), and hematocrit level, 40%. There was no defect in the clotting mechanisms of the blood, and examination of the bone marrow showed no abnormalities. The serum calcium was 10.2 mg. per 100 ml., inorganic phosphorus 4.8 mg. per 100 ml. and alkaline phosphatase 4 units. Several estimations of the serum protein and of the albumin:globulin ratio were within normal limits. An electro-

phoretic pattern was normal, revealing no increase in the serum globulin. Results of gastrointestinal studies, barium enema examination, proctoscopy, and esophagoscopy were normal. Gastroscopy showed changes suggesting mild atrophic gastritis. Biopsy of the gastric mucosa by the vacuum tube technique was interpreted as showing no abnormalities. An Einhorn "string test" indicated that the bleeding source was in the stomach. Gastric analysis revealed normal free and total acid before and after a test meal. A Hollander test was normal. X-ray survey of the skeleton revealed no bone lesions.

Hospital Course.—The tuberculin skin test was negative. Because of continued bleeding from the stomach, the patient was transferred to the surgical service, where, on Jan. 9, 1953, abdominal laparotomy was performed. The preoperative diagnosis was "hemorrhagic gastritis, possibly peptic ulcer." At operation the gastric mucosa was found to be friable and yellowish in color; it oozed considerably but no ulcer was found. A posterior gastroenterostomy and vagotomy were

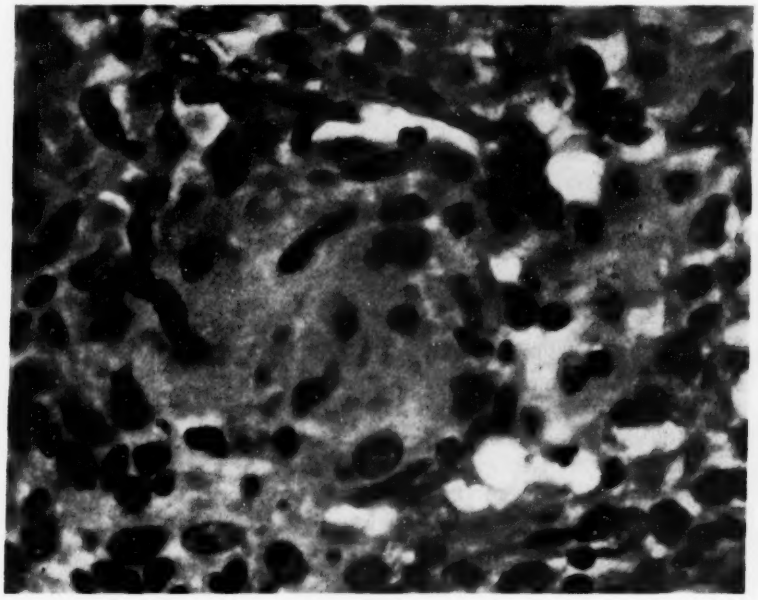

Fig. 4 (Case 2).—High power view of part of Figure 3, showing detail of one of the giant cells; × 660.

performed. Postoperative course was smooth, and the patient made a rapid recovery. He became asymptomatic, there was no further evidence of gastrointestinal bleeding, and he returned to military duty.

Microscopic examination of a biopsy specimen of the stomach taken at operation showed multiple foci epithelioid tissue containing giant cells in the gastric mucosa. There was no caseation and there were no inclusion bodies. These foci were interpreted as "compatible with lesions of sarcoid" (Figs. 3 and 4).

COMMENT

It is apparent that involvement of the gastric mucosa by these lesions produces no single clinical syndrome. No significant gastrointestinal symptoms were mentioned in several of the cases reviewed. The gastric sarcoid of four of the cases was found in association with benign gastric ulcer, so the symptoms were presumably due to that condition. In one case it was seen to be associated with polypoid carci-

noma of the stomach. What role, if any, the granulomatous lesions played in the production of the ulcers and carcinoma, or vice versa, is not clear.

Of the three cases in which hemorrhage was the chief clinical problem, one exhibited no demonstrable ulcer and in the second they were only small superficial gastric ulcerations. In the third, a typical duodenal ulcer was found, with erosion into the pancreaticoduodenal artery as the source of hemorrhage. Superficial gastric ulcerations, without clinical manifestations, were found in several other cases in which there was no hemorrhage.

More typical of sarcoid, clinically, were the four cases in which pyloric stenosis was manifested. An important characteristic of the disease is that symptoms, when they occur, seem to be chiefly the result of space occupancy and interference with function rather than of any pathophysiological process emanating from the sarcoid tissue. The end result of the granulomas is often fibrosis, which continues the physical interference with function. Obstruction of the pylorus in these patients was apparently the result of just such dense accumulation of sarcoid tissue. Involvement which is more diffuse produced the x-ray picture of linitis plastica in one case.

In none of the cases was the presence of sarcoid or sarcoid-like granulomas suspected prior to microscopic examination of the gastric mucosa. The diagnosis of the lesions on purely clinical grounds is not possible. In none of the cases in which it was done was gastroscopy of any assistance. X-ray examination offered no specific diagnostic information.

It is of interest that in all cases except one (our Case 2) in which the degree of gastric acidity was determined, free gastric acid was either of very low titre or absent. This occurred in several different types of cases—pyloric stenosis, suspected linitis plastica, concurrent polypoid carcinoma of the stomach, and in our first case, in which the symptoms and signs were very vague. Whether the sarcoid and sarcoid-like lesions involved the gastric mucosa because of its diminished ability to secrete acid, or whether the acidity was decreased because of the invasion of the lesions is not apparent. In our first case the mucosa between the granulomatous foci appeared normal and was presumably capable of secreting normal gastric juice, but such was not the case.

The study of these granulomas of the stomach necessarily stimulates an interest in other granulomas of the gastric mucosa. The more specific lesions, such as those produced by tuberculosis and syphilis, have assumed their logical niche in an organized system of pathology. Cohn, White, and Weyrauch [17] noted nonspecific granulomatous lesions in the gastric mucosa of a patient who had taken hydrated aluminum silicate (kaolin) over a long period because of duodenal ulcer. They fed kaolin to rabbits and produced similar lesions in the gastric mucosa of those animals. There are several references in the literature to cases of "nonspecific granulomas" of the stomach. [18] The exact relationship between such lesions and sarcoid and sarcoid-

17. Cohn, A. L.; White, A. S., and Weyrauch, H. B.: Kaolin Granuloma of the Stomach, J. A. M. A. **117**:2225-2227, 1941.

18. Erdmann, J. F., and Burt, C. V.: Non-Specific Granuloma of the Gastrointestinal Tract, Surg. Gynec. & Obst. **57**:71-80, 1933. Kolodny, A.: Infective Granuloma of the Stomach: Pseudocancer, Ann. Surg. **102**:30-33, 1935. Ortmayer, M.; Balkin, R., and Humphreys, E.: Chronic Erosive, Granulomatous, Atrophic Gastritis: A Case Report of a Rare Disease, Gastroenterology **6**:298-301, 1946. Vulliet, M. H.: D'un curieuse tumeur de l'estomac (granulome), Rev. méd. Suisse Rom. **40**:754-813, 1920.

like granulomas is not clear, and a study of the problem is planned for future publication. It is again pointed out that the histologic diagnosis of sarcoidosis is often difficult. Its etiology remains unknown. Reimann and Price [19] pointed out the similarity between sarcoidosis and histoplasmosis. Pinkerton and Iverson [20] reported three fatal cases of disseminated histoplasmosis diagnosed before death and at the time of autopsy as sarcoidosis. Later a review of the autopsy material revealed the presence of H. capsulatum (one of these three was the same case reported by Engle [1] and mentioned earlier in this paper). It is entirely possible that sarcoidosis as we know it is a nonspecific reaction of the body to several different etiological agents. Among these might be included the tubercle bacillus or an aberrant form thereof, H. capsulatum, Treponema pallidum, silica, beryllium, and talcum. It is not, however, the purpose of this paper to defend or to challenge sarcoidosis as a clinical and pathological entity. The 19 cases herein reviewed and the 2 new ones presented have been interpreted with the above considerations in mind, and it is believed that all fit into the pathologic category of "sarcoid or sarcoid-like granulomas."

SUMMARY

Involvement of the stomach by noncaseating sarcoid and sarcoid-like granulomas is not a common occurrence, and no single specific clinical syndrome stems from such involvement; indeed there are no symptoms in some cases. Dense accumulation of these lesions at the gastric outlet can result in pyloric obstruction, just as diffuse involvement of the gastric mucosa may give a linitis plastica-like picture. Sarcoid and sarcoid-like granulomas have been seen in association with diffuse bleeding from the gastric mucosa, benign gastric ulcer, polypoid carcinoma of the stomach, and typical duodenal ulcer with hemorrhage. The exact relationship of the sarcoid and sarcoid-like lesions to those clinical syndromes is not clear.

Confusion exists as to the exact place of these lesions with respect to other granulomatous lesions of proved etiology which may also invade the gastric mucosa, but it is believed that the 19 cases from the literature and the 2 new cases presented represent valid cases of sarcoid and sarcoid-like granulomas of the stomach.

19. Reimann, H. A., and Price, A. H.: Histoplasmosis Resembling Sarcoidosis, Tr. A. Am. Physicians **62**:112-115, 1949.

20. Pinkerton, H., and Iverson, S.: Histoplasmosis: 3 Fatal Cases with Disseminated Sarcoid-like Lesions, A. M. A. Arch. Int. Med. **90**:456-467, 1952.

ACUTE RELAPSING PANNICULITIS

Report of a Case of Weber-Christian Disease with Vascular Changes

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AND
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WE RECENTLY investigated a 27-year-old woman with an illness of 10 years' duration, consisting of recurrent acute episodes of fever, marked toxic symptoms, and excruciating muscular pains, associated with the exhibition of crops of subcutaneous lesions primarily involving the panniculus. These episodes, lasting from one to six months, were followed by periods of complete remission. Secondary causes of panniculitis were eliminated, and a thorough search for a possible etiologic agent was unsuccessful. The clinical impression of Weber-Christian disease was confirmed by tissue examination. The purpose of this report is to call attention to the acute variant of this syndrome and to the considerable vascular changes that were present.

CASE REPORT

F. B., a 27-year-old white single female secretary, enjoyed good health until the age of 18, at which time she apparently suffered an upper respiratory infection, associated with pain in the right ear. Shortly after this acute pains developed in the neck, back, legs, and arms. After a two-week interval, the first crop of subcutaneous lesions developed, first on the hands, and, several days later, generalized over the legs, thighs, and abdomen. These lesions were erythematous at the onset and later became violaceous. The patient was hospitalized in December 1942, and a biopsy of the nodules on the hand and thigh was done. The patient stated that she was told that the tissue examination revealed only inflammatory changes. After a spontaneous remission the patient again was well for about four months.

In April 1944, after a febrile illness consisting of diffuse pains, nausea, and vomiting, with high fever, there was recurrence of the skin lesions. At this time the patient was given a course of snake venom therapy, on the assumption that the lesions were of vascular origin and were associated with increased vascular fragility. Because of an adverse reaction no further therapy was instituted, and after an illness of six months the patient had a spontaneous remission, for the second time.

In October 1946, following an acute upper respiratory infection, she had her third relapse and was again hospitalized and various forms of therapy were administered unsuccessfully. From January to March 1947, she was again hospitalized, at which time an additional biopsy was done of a lesion of the left thigh. The patient was informed that the tissues showed inflammatory changes of the blood vessels. A complete allergy work-up was noncontributory. During this episode the patient had a continual low-grade fever and a course of typhoid therapy was instituted. Eventually she showed some improvement and was discharged.

Until the onset of the patient's illness menses had been regular and normal in duration and in amount. The first episode followed a normal period in October 1942. After this, there were periods of amenorrhea lasting 12 to 15 months. In 1947 a course of hormonal therapy consisting of estrogens and progesterone was given, which was followed by a single menstrual period. Shortly afterwards there followed the fourth relapse, which lasted four weeks.

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The fifth relapse occurred in October 1947, again shortly after an upper respiratory infection, in this instance complicated by a conjunctivitis. The patient was again hospitalized, and a second course of typhoid vaccine and tripelennamine (Pyribenzamine) was administered, without dramatic effects. Following the spontaneous remission a second course of hormonal therapy, plus ascorbic acid, was administered. During this course of therapy the patient suffered her sixth relapse. A biopsy of another lesion was performed, and apparently there was no specific diagnosis established, and a repeated biopsy at still another institution was not diagnostic. The patient was again informed that some form of collagen disease was suspected and was discharged to continue therapy on an ambulatory basis. Shortly thereafter, marked swelling of the joints of the fingers developed. The patient was then given a course of antireticular cytotoxic serum (ACS) over several months, with some apparent improvement. Since this single episode there have been no further joint complaints. The seventh relapse occurred in November 1948 after an upper respiratory infection. After the patient was rehospitalized, a third course of typhoid vaccine and tripelennamine was instituted and the process promptly subsided.

The patient remained well until February 1951, when the eighth relapse occurred, following an upper respiratory infection. She was hospitalized for a 10-day course of corticotropin (ACTH). After her discharge, she continued to take cortisone, and in July of 1951 she again had a remission.

The patient was observed by one of us (S. L.) during her ninth relapse, in Miami Beach, Fla., Jan. 20, 1952, one week after an upper respiratory infection. Nausea, vomiting, and diffuse pains in the legs, neck, and back developed. Because of the marked prostration, weakness, and severe pains in the extremities, a diagnosis of neurotropic virus infection was considered. The patient was admitted to the Mount Sinai Hospital on Jan. 22, 1952. Physical examination on admission revealed an acutely ill, febrile, toxic-appearing, well-developed, and well-nourished woman of 27. The skin revealed a reddish-blue discoloration over the right deltoid region, and there was an exquisitely tender ill-defined nodular mass, approximately 2 cm. in diameter, in the right trapezius area. There was no evidence of atrophy, scarring, excoriations, or rash. Over the lower abdomen and thighs there appeared to be an excessive deposition of fat, and the skin over this area showed red striae. There was no jaundice or petechiae present. The skull was symmetrical. The pupils were equal and reacted to light and in accommodation. The extraocular motions were normal. The nose revealed no obstruction or discharge; there was no sinus or mastoid tenderness. The mouth and pharynx revealed no evidence of inflammation, ulceration, or abnormal pigmentation. The trachea was in the midline. The thyroid was not enlarged, and there was no adenopathy. The chest was symmetrical, and the breasts were normal. The heart was not enlarged to percussion, and the heart sounds were regular and of good quality. The blood pressure was 120/80. There were no murmurs audible. The lungs were clear to percussion and auscultation. The abdomen revealed no evidence of tenderness, spasm, or masses. The liver, spleen, and kidneys were not palpable. Rectal and pelvic examinations revealed no abnormalities. The lower extremities revealed marked hyperaesthesia of the skin, with diffuse tenderness of the leg and thigh muscles. The reflexes were physiologic. There was no edema or clubbing.

The initial blood count revealed a white cell count of 18,550, with 57% polymorphonuclear cells, 38% lymphocytes, 3% band forms, and 2% monocytes. Platelets were present. The red blood cell count was 4,970,000, with 12.7 gm. of hemoglobin. The urine had a specific gravity of 1.033, with a trace of albumin and 1 to 4 pus cells. Results of the serology studies were negative. The prothrombin time was 15 seconds; the control was 14 seconds. The clotting time (Lee-White) was 8 minutes, and clot retraction was normal. The total protein was 6.63 gm. per 100 cc. The albumin was 4.38 gm. and the globulin 2.25 gm. per 100 cc. The van den Bergh test showed 0.69 mg. bilirubin per 100 cc. The urea nitrogen was 15.4 mg. per 100 cc. The cephalin flocculation test, both at 24 and at 48 hours, was negative. The total cholesterol was 213 mg. and the cholesterol ester was 159 mg. per 100 cc. The electrocardiogram was within normal limits.

Following admission the patient was acutely ill with marked prostration, complaining of severe pains in the extremities, back, and neck. The disease ran a febrile course, with daily temperature elevation up to 101 F. rectally. During this period new skin lesions developed over

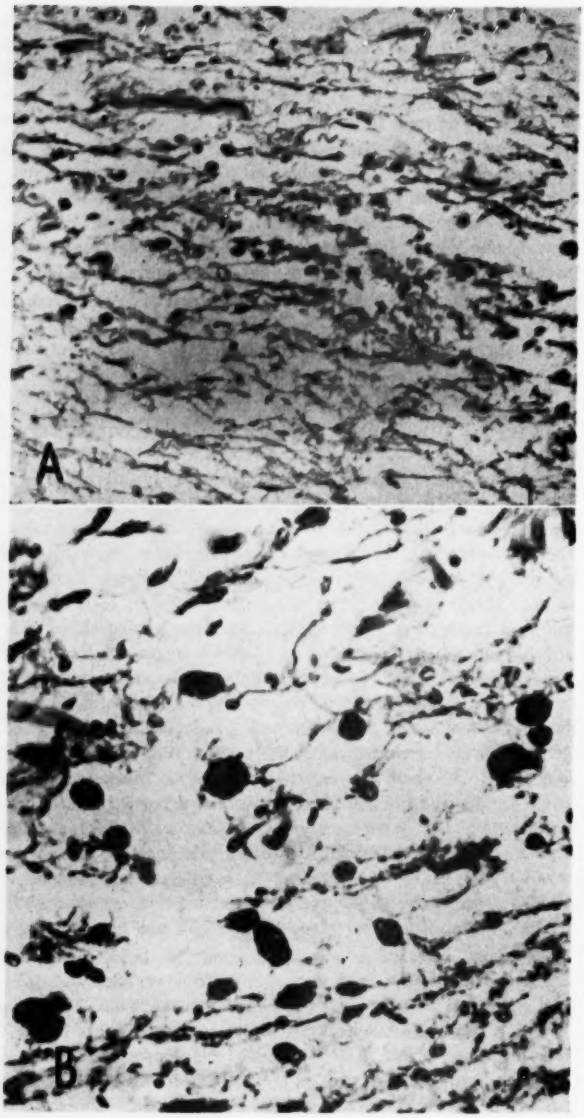

Fig. 1.—*A*, subcutaneous fat tissue, showing irregularity and collapse of fat cells, with granularity and fraying of septa and infiltration of small macrophages. Hematoxylin and eosin stain; × 68. *B*, the same; × 456.

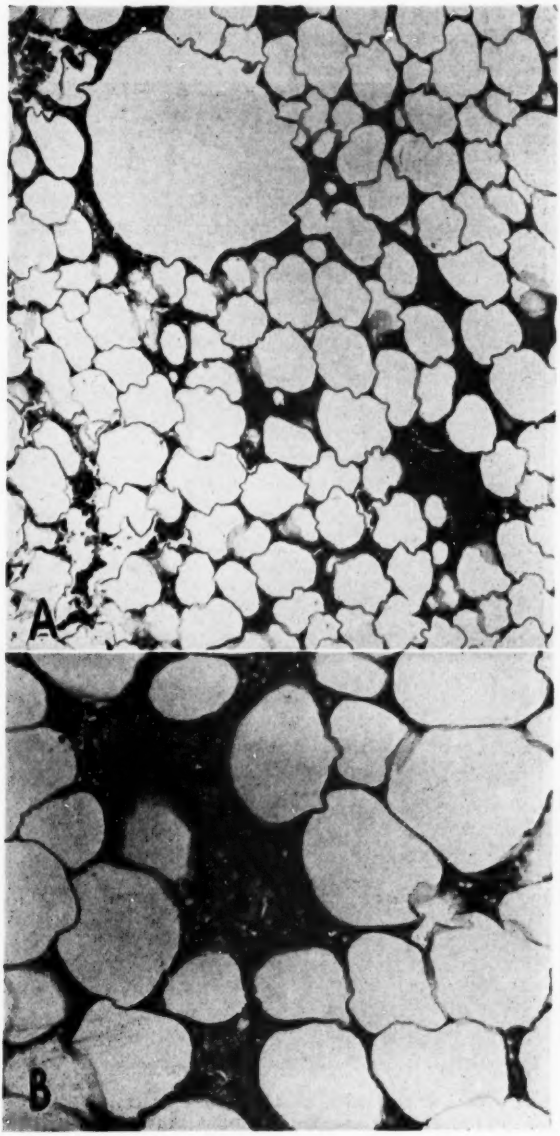

Fig. 2.—*A*, subcutaneous fat tissue, showing large fat spaces, with an infiltration of red cells. Hematoxylin and eosin stain; × 85. *B*, subcutaneous fat tissue, showing large lipid-containing macrophages. Hematoxylin and eosin stain; × 200.

the abdomen and thighs and one developed in the breast. The patient was started on antibiotic therapy, chloramphenicol (Chloromycetin) 250 mg. every three hours. In addition she was given cortisone, 200 mg. per day, and ascorbic acid, 1,000 mg. per day. Although the temperature returned to normal, nodules continued to appear in crops, associated each time with constitutional

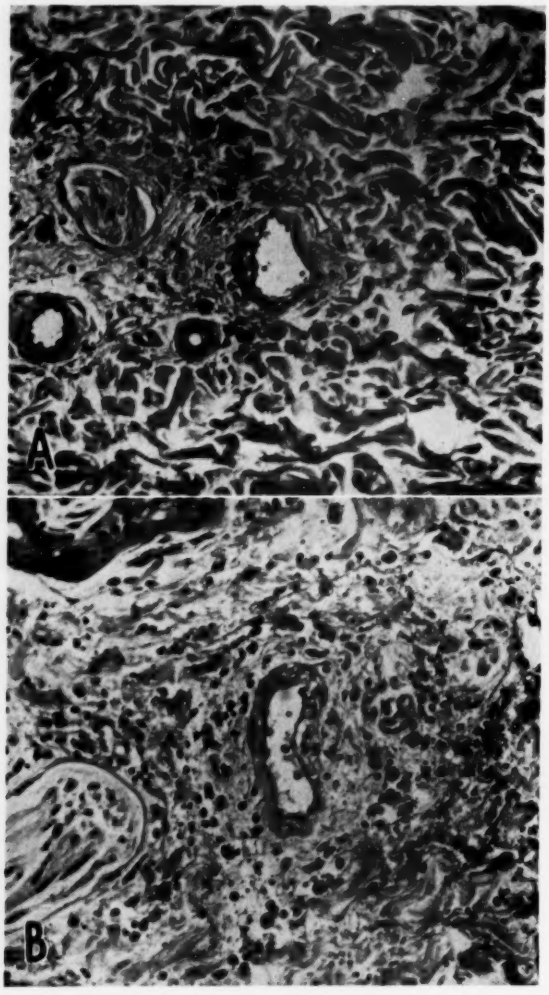

Fig. 3.—*A*, derma, showing irregularity of staining of collagen. A venule is seen, with degeneration of the wall and moderate perivascular infiltration. An arteriole is seen showing minimal perivascular infiltration. Hematoxylin and eosin stain; × 200. *B*, derma, showing degeneration of wall of venule, with infiltration of lymphoid cells around venule, sweat gland, and nerve fiber. Hematoxylin and eosin stain; × 200.

symptoms. On the 10th hospital day, the patient was seen by the consultant in dermatology, Dr. Lewis Capland, who suggested the diagnosis of Weber-Christian syndrome. In view of the

beneficial effects on this condition reported by Arnold,[1] the patient was started on sulfapyridine, 2 gm. a day. Cortisone was continued without appreciable effect for a total of 19 days in doses varying from 100 to 200 mg. per day.

Despite therapy new lesions continued to appear, although at a slower rate. A skin biopsy was performed through a fresh lesion. Results of capillary fragility tests on two occasions were normal. The platelet counts were normal (250,000). The white cell count remained within

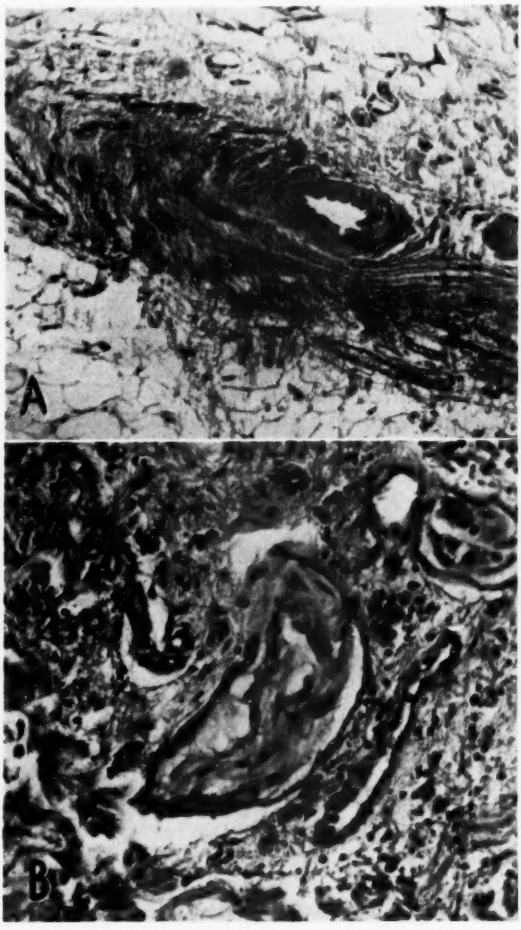

Fig. 4.—*A*, subcutaneous fat, showing small artery with necrosis of one part of its wall fusing with altered surrounding collagen. Hematoxylin and eosin stain; × 78. *B*, nerve fiber, showing degenerative changes. Hematoxylin and eosin stain; × 200.

normal limits after the initial leukocytosis, and the urinary findings were normal. By the end of the third week there was evidence of a slow remission and the patient was discharged, to continue therapy on an ambulatory basis.

1. Arnold, H. L., Jr.: Nodular Nonsuppurative Panniculitis (Weber-Christian Disease): Preliminary Report of a Case Controlled by Sulfapyridine, Arch. Dermat. & Syph. **51**:94-99, 1945.

For the next five weeks sulfapyridine therapy was continued, and except for the appearance of one or two fresh nodules each week the patient felt fairly well. Two days after she was chilled in an air-conditioned room the 10th relapse developed. She became acutely ill, with severe constitutional symptoms of diffuse pains, nausea, vomiting, and dehydration, associated with the appearance of multiple nodules from 0.5 to 3 cm. in size. She was readmitted to Mount Sinai Hospital for corticotropin therapy. On this admission it was apparent that corticotropin produced a good response, and on the seventh day it was discontinued. The following day three new lesions appeared. On the basis of the appearance of the biopsy specimen, one of us (M. L.) suggested therapy with a peripheral vasodilator, namely benzazoline (Priscoline) hydrochloride 25 mg. every four hours. Following this there were no new lesions and the improvement became obvious. This episode was the shortest in duration, despite the fact that the onset was very severe. Further laboratory investigation, including blood cultures, rabbit and guinea pig inoculations of blood and serum, routine agglutination studies, determination of serum protein partition, and determinations of Goffman body and lipid fractions, revealed no abnormalities.

After the patient was discharged from the hospital, the nodules involuted from slightly elevated painful violaceous lesions to a more bluish color, with gradual diminution in size. One or two nodules remained palpable as small firm nodes, but at no time did the patient display the dimpling, or scooped out, saucer-like effect seen in the patients reported by Cummins [2] and others. At the time of this writing, the patient has remained well for 13 months. She has continued on benzazoline as her only therapy.

Pathologic Examination.—Gross Description: The specimen consisted of a segment of skin, measuring 4 cm. in greatest dimension, with attached underlying fat tissue extending downward for a distance of 4 cm. Part of the tissue was fixed in 4% formaldehyde solution, and part in Zenker's solution. Sections were stained with hematoxylin and eosin, Weigert's elastic tissue stain counterstained with Van Gieson's connective tissue stain, Hortega's reticulum stain, Hotchkiss' glycoprotein stain, and Mallory's connective tissue stain.

Microscopic Examination: The outstanding pathologic changes were found in the subcutaneous fat and, to a lesser extent, in the derma. The fat cells were often collapsed and in some cases were fused into larger amorphous masses (Figs. 1 and 2*A*). The septa between the fat cells were irregular, in spots frayed, granular, and focally destroyed. There was a focal infiltration of neutrophiles, red cells, or large and small macrophages throughout the fat tissue (Figs. 1*B* and 2). In the derma, the collagen was focally more deeply eosinophilic and swollen, but it was not sufficiently changed to be termed "fibrinoid degeneration" (Fig. 3*A*). The venules of the corium and subcutaneous tissue showed degeneration of their walls and infiltration with lymphoid cells and neutrophiles (Fig. 3). A few microscopic arteries showed degeneration of the muscularis and the collagen of the adventitia (Fig. 4*A*). There was an infiltration of neutrophiles and mononuclear cells around the arterioles and venules of the corium, as well as around the skin appendages (Fig. 3*B*). The large microscopic arteries and veins and the epithelium showed no change. The nerve elements in the corium showed swelling and vacuolization (Fig. 4*B*).

The pathologic diagnosis was acute focal pannicular necrosis with acute venulitis and perivasculitis of the subcutaneous fat and corium.

COMMENT

Relapsing nodular nonsuppurative panniculitis was first described by Weber [3] as a clinical entity in 1925. Since then, about 60 cases have been reported. Christian [4]

2. Cummins, L. J., and Lever, W. F.: Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian's Disease): Report of 2 Cases, Arch. Dermat. & Syph. **38**:415-426, 1938.

3. Weber, F. P.: Relapsing Non-Suppurative Nodular Panniculitis Showing Phagocytoses of Subcutaneous Fat Cells by Macrophages, Brit. J. Dermat. **37**:301-311, 1925.

4. Christian, H. A.: Relapsing Febrile Nodular Nonsuppurative Panniculitis, Arch. Int. Med. **42**:338-351, 1928.

added febrile to the descriptive title of the syndrome in 1928. Excellent reviews by Bendel,[5] in 1949, and Shuman,[6] in 1951, have adequately summarized the world literature.

The characteristic clinical features of Weber-Christian disease suggest a distinct form of panniculitis. The onset of fever, with temperature elevation up to 101 to 103 F., or even higher, and severe constitutional symptoms, followed by the appearance of crops of painful subcutaneous nodules on the arms, breasts, abdominal wall, thighs, and legs, occurring in episodic manner with intervening periods of complete remission, lead to the diagnosis. The nodules first appear as subcutaneous swellings of varying size. These swellings gradually become more discrete, the overlying skin becoming first reddened and then a deeper, more violaceous color. Ulceration of the skin is rare. Larger nodules of a more chronic nature result in atrophy of the fat, causing a saucer-like appearance, or "dimpling." In Weber's [3] case and in other typical reported cases,[7] as well as in ours, there was no evidence of atrophy on healing of the nodules.

The differential diagnosis of Weber-Christian disease from other forms of panniculitis secondary to local injury to the panniculus, acute sepsis, sclerosing lymphogranuloma, fat necrosis of the breast,[8] and the various nodular vascular diseases of the legs [9] can usually be made by a careful clinical appraisal, whereas the biopsy specimen may often be indistinguishable in many of these conditions. The disease is rarely fatal, and in the cases in which autopsy was done [10] there was conspicuous lack of uniformity of findings.

The fundamental pathologic change is found in the subcutaneous adipose tissue, with minimal changes in the corium and epithelium. There is no known associated involvement of other organs in the acute process. The adipose tissue shows destruction and collapse of the fat cells, their septa usually remaining intact. There is an intense infiltration of mononuclear cells, lymphocytes, and macrophages, in addition to neutrophiles, eosinophiles, and plasma cells. The corium shows slight inflam-

5. Bendel, W. L., Jr.: Relapsing Febrile Nodular Panniculitis (Weber-Christian Disease): Review of Literature and Report of Case, Arch. Dermat. & Syph. **60**:570-596, 1949.

6. Shuman, C. R.: Relapsing Panniculitis (Weber-Christian Disease): Review of Literature and Report of Case Including Treatment with Cortisone, A. M. A. Arch. Int. Med. **87**:669-681, 1951.

7. Bunnell, I. L., and Levy, D. S.: Weber-Christian's Disease: Report of Case, Ann. Int. Med. **28**:169-172, 1948. Rubin, S. H., and Bland, J. H.: Relapsing Febrile Non-Suppurative Panniculitis (Weber-Christian Disease), Am. J. Med. **7**:288-292, 1949.

8. Smetana, H. F., and Bernhard, W.: Sclerosing Lipogranuloma, Arch. Path. **50**:296-325, 1950.

9. Montgomery, H.; O'Leary, P., and Barker, N. W.: Nodular Vascular Diseases of the Legs: Erythema Induratum and Allied Conditions, J. A. M. A. **128**:335-341, 1945. McGovern, T., and Wright, I. S.: Pernio: a Vascular Disease, Am. Heart J. **22**:583-606, 1941.

10. (*a*) Tilden, I. L.; Gotshalk, H. C., and Avakian, E. V.: Relapsing Febrile Non-Suppurative Panniculitis: Report of 2 Cases, Arch. Dermat. & Syph. **41**:681-689, 1940. (*b*) Miller, J. L., and Kritzler, R. A.: Nodular Nonsuppurative Panniculitis, ibid. **47**:82-96, 1943. (*c*) Spain, D. M., and Foley, J. M.: Nonsuppurative Nodular Panniculitis (Weber-Christian's Disease) Am. J. Path. **20**:783-787, 1944. (*d*) Friedman, N. B.: Fatal Panniculitis, Arch. Path. **39**:42-46, 1945. (*e*) Ungar, H.: Relapsing Febrile Nodular Inflammation of Adipose Tissue (Weber-Christian Syndrome): Report of a Case with Autopsy, J. Path. & Bact. **58**:175-185, 1946. (*f*) Mostofi, E. K., and Engleman, E.: Fatal Relapsing Febrile Nonsuppurative Panniculitis, Arch. Path. **43**:417-426, 1947.

matory changes around the appendages and in the contained fat. In a minority of cases fibrinoid changes have been observed in the connective tissue. In the chronic lesions nonspecific granulomatous inflammation of fat tissue is seen.

Vascular changes of two types have been found.[11] In one type the arterioles and venules show perivascular infiltration, with or without endothelial swelling, and thickening of the walls. In the other type true fibrinoid degeneration of the small vessel walls occurred. A scant inflammatory change around the nerves has also been noted.

From the pathologic standpoint, our case falls into the pattern of an acute panniculitis, with areas of pannicular necrosis, accompanied by venulitis, arteriolitis, and nerve degeneration. The amount of inflammatory exudate was less than that found in most cases of Weber-Christian disease, and the lesion showed no evidence of chronicity and granuloma formation.[11b] On the other hand, the vasculitis of the corium and subcutaneous tissue was more severe than that seen in most cases of nonsuppurative panniculitis. It is interesting to note the presence of degeneration of nerve endings, as seen in the biopsy specimen. Stockman [12] and others previously described nerve involvement. This closely correlates with one of the outstanding clinical complaints in our case, ushering in each new episode, namely, the marked pain and hyperaesthesia.

During our patient's 10-year illness, the possibility of some form of specific collagen disease was considered most likely. The various biopsy studies done previously were not available to us. Our biopsy specimen, taken through a fresh lesion, revealed that while both collagen and vascular involvement were present in the acute inflammatory process, the predominant pathologic change lay in the fat tissue. A plasma L. E. preparation made during a previous acute episode was reported negative. We therefore feel that we are dealing with an acute form of Weber-Christian disease with vascular-collagen changes.

A thorough search was made for a possible etiologic agent. Blood cultures were repeatedly negative, as in most of the reported cases. Some cases of panniculitis have been definitely associated with either localized sepsis or proved septicemia.[10b,d] In our minds, these represent a suppurative type of panniculitis which runs the course of the acute septic process and hence would respond to the specific antibiotics.[13] Duran-Reynals,[14] in 1946, reported an epidemic-like disease in rabbits, which resembled human Weber-Christian disease. We unsuccessfully attempted to reproduce the disease in two rabbits and two guinea pigs by inoculation of our patient's blood and serum during both the acute and the chronic phase of the disease.

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11. (*a*) Alderson, H. E., and Way, S. C.: Relapsing Febrile Nonsuppurative Panniculitis (Weber), Arch. Dermat. & Syph. **27**:440-449, 1933. (*b*) Gilchrist, T. C., and Ketron, L. W.: A Unique Case of Atrophy of the Fatty Layers of the Skin Preceded by the Ingestion of Fat by Large Phagocytic Cells; Macrophages, Bull. Johns Hopkins Hosp. **26**:291-294, 1916. (*c*) Cummins and Lever.[2] Shuman.[6] Tilden, Gotshalk, and Avakian.[10a]

12. Stockman, R.: The Clinical Symptoms and Treatment of Chronic Subcutaneous Fibrosis, Brit. M. J. **1**:352-355, 1911.

13. Zee, M. L.: Nodular Nonsuppurative Panniculitis Treated with Penicillin, J. A. M. A. **130**:1219-1220, 1946.

14. Duran-Reynals, F.: A Necrotizing Disease in Rabbits Affecting Fatty and Muscular Tissues: Analogies with Weber-Christian Disease of Humans, Yale J. Biol. & Med. **18**:583-594, 1946.

Halogens were originally thought to be causative in some cases,[15] bromides being the most often implicated. There was no history of any type of food or drug intolerance in our case. Allergy has been suggested as a possible cause.[16] As previous studies indicated, we found no evidence of systemic allergy. The absence of eosinophilia in the peripheral blood and biopsy specimen did not, however, exclude some form of hypersensitivity reaction, as was suggested by the sequence of relapse following severe respiratory infections.

Our studies of the blood lipids, including phospholipids, cholesterol and cholesterol esters, and Goffman bodies, gave results which were within the normal range, as is consistent with other reported studies. This would not indicate that there was a basic metabolic disorder of fat.[17] The results of our studies of the liver, the serum protein fractions, and the alpha, beta, and gamma globulin, were all normal.

The clinical pattern suggested possible embolic or thrombotic lesions in the panniculus. The possibility of thrombocytic acroangiothrombosis[18] was excluded by the absence of vascular thrombi histologically and the normal platelet counts. The normal bleeding and clotting mechanism and normal capillary fragility, as well as reported bone marrow studies, served to exclude the hemopoetic system.

Various therapeutic agents have been reported as helpful, but none consistently. In reported cases patients with Weber-Christian disease have responded to sulfapyridine and to penicillin. Our patient was treated liberally with various antibiotics with no effect and was maintained on sulfapyridine, during which time an acute exacerbation occurred. Large amounts of ascorbic acid were administered without any appreciable effect. She previously had been treated with both cortisone and corticotropin with equivocal results. In our hands, however, corticotropin produced a beneficial effect, which was more evident than with cortisone. We also administered the vasodilator benzazoline, 25 mg. every four hours, because of the vascular changes noted histologically. No lesions occurred after this administration. This may be a purely fortuitous coincidence. It is, however, possible that in some cases a favorable result may be obtained by the use of corticotropin with or without a vasodilator.

SUMMARY

A case of acute relapsing panniculitis of 10 years' duration is presented. An unsuccessful search for an etiologic agent was made. It is suggested, on the basis of biopsy and clinical studies, that this case represents an acute variant of Weber-Christian disease with vascular-collagen changes. Treatment with corticotropin (ACTH) with or without a vasodilator may be of benefit in cases of this type.

15. (*a*) Charache, H.: Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Syndrome), New York J. Med. **52**:1133-1136, 1952. (*b*) Bailey, R. J.: Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Disease), J. A. M. A. **109**:1419-1425, 1937.

16. Eisaman, J. L., and Schneider, L. A.: Nodular Nonsuppurative Panniculitis (Weber-Christian Disease), J. A. M. A. **146**:1417-1418, 1951. Shuman.[6] Bailey.[15b]

17. Wells, H. G.: Adipose Tissue: A Neglected Subject, J. A. M. A. **114**:2177, 1940. Wertheimer, E., and Shapiro, B.: The Physiology of Adipose Tissue, Physiol. Rev. **28**:451-464, 1948. Shuman.[6]

18. Tacket, H. S., and Jones, R. S.: Thrombocytic Acroangiothrombosis. Febrile Anemia: Thrombocytopenia; and Thromboses of Damaged Capillaries and Arterioles, Circulation **5**:920-926, 1952.

ACUTE ABDOMINAL CONDITION DUE TO BISHYDROXYCOUMARIN (DICUMAROL) POISONING

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AND
ARNOLD IGLAUER, M.D.
CINCINNATI

THE NUMBER and variety of the complications as a result of bishydroxycoumarin (Dicumarol) intoxication, or poisoning, are of staggering proportions. A review of the literature leads one to conclude that in this drug one is dealing with a truly fine pharmaceutical tool but one that without proper surveillance may easily become a lethal weapon. In the report of a fatal case of bishydroxycoumarin poisoning Duff and Shull [1] state succinctly:

> The most important of all contraindications to the use of dicumarol® is lack of reliable laboratory facilities for prothrombin determinations. Employment of this beneficial drug without laboratory control is hazardous and may result in fatal widespread hemorrhage.

Aggeler [2] has collected and tabulated from the American literature the number of hemorrhagic complications following bishydroxycoumarin therapy up to 1946. He reports that of a total of 1,471 patients treated with the drug hemorrhagic complications developed in 123 (8.3%). There were five deaths (0.34%) among those treated, in which bishydroxycoumarin therapy was definitely implicated. Others [3] reviewing large series of cases report bleeding of varying degree of 6.4%, with major bleeding from the gastroenteric tract in 1.8% of cases.

The histopathologic findings and changes in such cases of overdosage of the drug are held chiefly due to serious damage to blood vessels and hemorrhages into various organs and tissues. Bingham and his associates [4] report that in animals dying acutely after the administration of massive doses of bishydroxycoumarin the histologic picture is one of dilatation of the capillaries and of the small arteries and veins. This observation is confirmed by Shlevin and Lederer.[5]

In the voluminous literature there are reported various types of bleedings, many of a bizarre and unique character, with interspersed instances of intraperitoneal

From the Departments of Surgery and Internal Medicine, The Jewish Hospital.

1. Duff, I. F., and Shull, W. H.: Fatal Hemorrhage in Dicumarol Poisoning: With Report of Necropsy, J. A. M. A. **139**:762-766 (March 19) 1949.

2. Aggeler, P.: Heparin and Dicumarol—Anticoagulants: Their Prophylactic and Therapeutic Uses, California Med. **64**:71, 1946.

3. Allen, E. V.; Hines, E. A., Jr.; Kvale, W. F., and Barker, N. W.: The Use of Dicumarol as an Anticoagulant: Experience in 2,307 Cases, Ann. Int. Med. **27**:371-381 (Sept.) 1947.

4. Bingham, J. B.; Meyer, O. O., and Pohle, F. J.: Studies on the Hemorrhagic Agent, 3, 3'-methylenebis (4-hydroxycoumarin): I. Its Effect on the Prothrombin and Coagulation Time of the Blood of Dogs and Humans, Am. J. M. Sc. **202**:563-578 (Oct.) 1941. McCarter, J. C.; Bingham, J. B., and Meyer, O. O.: Studies on the Hemorrhagic Agent, 3, 3'-methylenebis (4-hydroxycoumarin): IV. The Pathologic Findings After the Administration of Dicumarol, Am. J. Path. **20**:651-659 (May) 1944.

5. Shlevin, E. L., and Lederer, M.: Uncontrollable Hemorrhage After Dicoumarol Therapy with Autopsy Findings, Ann. Int. Med. **21**:332-342 (Aug.) 1944.

hemorrhage.[6] However, we do not feel that the picture of such bleeding masquerading in the guise of an acute abdominal condition has been forcefully brought to the attention of the medical profession. Recently we have encountered two such instances which impel us to report this deceptive abdominal complication.

CASE 1.—M. F., a 64-year-old white man, had a "thrombophlebitis some years ago," and in December 1951 repeated pulmonary emboli developed, at which time bishydroxycoumarin therapy was started. It was known that on March 31, 1952, he had a prothrombin level of 8%, 45 seconds, and that he was symptomless at that time. The dose was reduced from 75 mg. to 50 mg. per day.

On April 4, 1952, he experienced abdominal cramps and failure to move his bowels or pass gas. Although symptoms persisted, he did not consult his physician until two days later. At that time, examination revealed the patient to be pale and anxious. Blood pressure was 120/80, with a pulse rate of 120. There was right shoulder pain, hiccup, and pain on deep inspiration. The abdomen was tender and distended, with no audible peristalsis. The urine was grossly bloody. Synkavite, a water-soluble vitamin K analogue, was given intravenously at once in dosage of 75 mg., and the patient was taken to the hospital. At the hospital 1 unit of plasma was administered plus 500 mg. of vitamin K_1 intramuscularly and 500 mg. orally.

A flat plate of the abdomen revealed dilated loops of small bowel; no free air was seen. Because of the increasing abdominal distention and accompanying vomiting, surgical consultation was held and passage of a Cantor tube recommended.

On April 8, the abdomen was still distended and tender and there was rebound tenderness. The Cantor tube had progressed 5 to 6 feet (150 to 180 cm.). Frank hematuria was still present.

Because of x-rays now consistent with small bowel obstruction (according to the x-ray report on April 9, "the persistent distention [four days] of what appears to be the same small bowel loops over a period of four days with absence of any appreciable amount of gas in the colon lends support to a clinical diagnosis of mechanical obstruction") together with physical signs compatible with this diagnosis, operative intervention was advised. The prothrombin at this time was at a safe level for surgery.

Exploratory laparotomy was therefore performed on April 10, 1952. The operative note records that between 250 and 500 cc. of unclotted blood was found in the peritoneal cavity. The entire serosa of the small bowel was hemorrhagic. Oozing was seen from the small bowel mesentery at one point, and this was controlled with moist hot laparotomy pads. No obstruction was found.

CASE 2.—Mrs. I. C., a 44-year-old (quintipara) housewife, was admitted to the hospital on the evening of Nov. 11, 1952, because of right lower quadrant pain, vomiting, and obstipation. The pain had originated at 2:30 a. m. of the day of admission, was at first epigastric, and became residual in the right lower quadrant. The past history revealed hospital admissions for rheumatic fever and congestive failure and numerous admissions for pulmonary infarction. Owing to the heart condition a tubal ligation and interruption of tubal pregnancy had been performed four years previously at another institution, but incidental appendectomy had not been done. The patient was being treated with bishydroxycoumarin at home and was told to report to the outpatient dispensary weekly for prothrombin determinations. However, since she attached no particular importance to these weekly tests, she had failed to return to the clinic for the month prior to the present illness.

Examination revealed the patient to be acutely ill. The abdomen was diffusely tender, with maximum tenderness in the right lower quadrant. There was considerable right rectus muscle spasm, with splinting and rebound tenderness. There was no shoulder pain. Vaginal and rectal examinations revealed essentially normal conditions except for tenderness.

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6. Lilly, G. D., and Lee, R. M.: Complications of Anticoagulant Therapy, Surgery **26**: 957-969 (Dec.) 1949. Applebaum, I. L., and Shulman, P.: Dicumarol Poisoning: Report of a Case, J. M. Soc. New Jersey **46**:28-30 (Jan.) 1949. Thorsén, G.: Dicoumarol Poisoning with Relapse: Report of a Case, Lancet **2**:420-422 (Sept. 20) 1947.

The temperature was 99.8 F., and the pulse rate 90. Laboratory findings were as follows: the white blood cell count was 12,600, with 81% polymorphonuclear leucocytes. The hemoglobin was 14.5 gm., the red blood cell count 4,100,000, and prothrombin level reported as zero. The urine was dark amber, with a specific gravity of 1.028 and a reaction for sugar of 1 +; tests were positive for acetone and negative for albumin and there were occasional red blood and pus cells. Serum amylase was 225 Somogyi units. An flat x-ray of the abdomen revealed several loops of small bowel filled with air, stool in the colon, and no renal stone.

Several diagnoses were entertained, namely, acute appendicitis, partial intestinal obstruction, and possible intraperitoneal hemorrhage due to bishydroxycoumarin poisoning.

Vitamin K_1, 100 mg., was administered intravenously, and 1 unit of blood was secured.

In order to establish accurately a diagnosis of intraperitoneal hemorrhage due to bishydroxycoumarin poisoning as rapidly as possible, it was decided to use a technique frequently used in the determination of obscure and questionable cases of ruptured ectopic pregnancy, namely cul-de-sac puncture and aspiration. This was done the evening of admission, and liquid blood was withdrawn, thus conclusively demonstrating the diagnosis of free blood in the peritoneal cavity. Symptoms cleared without further therapy.

SUMMARY AND CONCLUSIONS

Two cases are reported of bishydroxycoumarin (Dicumarol) poisoning, in which the predominant early clinical findings were those of an acute abdominal condition.

In one instance either the clinician failed to impress the patient with the importance of returning at regular intervals for prothrombin determinations or else the patient's low mentality should have warned against such reliance being placed upon her.

In cases of suspected hemoperitoneum due to bishydroxycoumarin intoxication immediate prothrombin levels should, of course, be ascertained. Cul-de-sac aspiration in addition offers a simple method of corroborating the diagnosis.

News and Comment

ANNOUNCEMENTS

Award for Outstanding Research in the Field of Sterility for the Year 1954.—The American Society for the Study of Sterility announces the opening of the 1954 contest for the outstanding contribution to the subject of infertility and sterility. The winner will receive a cash award of $1,000, and the essay will appear on the program of the 1954 meeting of the Society. Essays submitted in this competition must be received not later than March 1, 1954.

For full particulars concerning requirements of this competition, address The American Society for the Study of Sterility, % Dr. Herbert H. Thomas, Secretary, 920 S. 19th St., Birmingham, Ala.

Second Annual Cancer Seminar.—Edward H. Bergman, M.D., Chairman of the Arizona Division of the American Cancer Society, announces the dates of the Second Annual Cancer Seminar, to be presented Jan. 14, 15, and 16, 1954, at Phoenix, Ariz.

Paradise Inn will again be headquarters, with all sessions held in the convention hall. Registrants will be housed at the Inn or at other adjoining resort hotels in the Camelback Mountain area.

The program is planned as a series of panel discussions by noted specialists. Topics to be presented are "Recent Advances in Cancer Therapy," "Neoplasms of the Central Nervous System," "Carcinoma of the Cervix," "Carcinoma of the Breast," "Exfoliative Cytology," "Surgical Methods for Relief of Intractable Pain," "Carcinoma of the Lung," "Trends in Cancer Research," "Leukemia and Lymphomas," and "Tumors of Childhood."

Participating in these discussions will be Paul C. Aebersold, Ph.D., of the Atomic Energy Commission, Oak Ridge, Tenn., Percival Bailey, M.D., University of Illinois College of Medicine, Chicago; O. A. Brines, M.D., Wayne University College of Medicine, Detroit; Charles S. Cameron, M.D., Medical and Scientific Director, American Cancer Society, New York; Anthony Curreri, M.D., University of Wisconsin Medical School, Madison, Wis.; Michael DeBakey, M.D., Baylor University College of Medicine, Houston, Texas; L. H. Garland, M.D., Stanford University School of Medicine, San Francisco; E. S. Gurdjian, M.D., Wayne University College of Medicine, Detroit; Joe Vincent Meigs, M.D., Harvard Medical School, Boston; Eugene P. Pendergrass, M.D., University of Pennsylvania School of Medicine, Philadelphia; Orvar Swenson, M.D., Tufts College Medical School, Boston, and David A. Wood, M.D., Director of the Cancer Research Institute, San Francisco.

Arizona men, serving as Moderators, will be Drs. Ralph Fuller, Edward M. Hayden, and Hugh Thompson, all of Tucson, and Preston T. Brown, John A. Eisenbeiss, Douglas Gain, John R. Green, D. W. Melick, and O. O. Williams, of Phoenix.

For reservations write to the Arizona Division, American Cancer Society, 1429 N. 1 St., Phoenix, Ariz.

PERSONAL NEWS

Dr. Daft Appointed Director of National Institute of Arthritis and Metabolic Diseases.—The appointment of Dr. Floyd S. Daft as Director of the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, was announced today by Dr. Leonard A. Scheele, Surgeon General of the Public Health Service, Department of Health, Education, and Welfare.

Dr. Daft, Acting Director of the Institute since the resignation of Dr. Russell M. Wilder last June, had been Assistant Director and Chief of Laboratory Research since 1951. He has been a member of the scientific staff of the National Institutes of Health, principal research arm of the Public Health Service, since 1937. He has directed and conducted nutrition studies, particularly on the B vitamins, and his investigations have contributed importantly to the

understanding of dietary deficiencies causing anemia, cirrhosis of the liver, and other metabolic diseases. He was a pioneer in the study of an unidentified substance later shown to be folic acid, a vitamin used widely today in the treatment of blood disorders.

Before coming to the National Institutes of Health, in 1937, Dr. Daft taught and engaged in research work at Harvard, Yale, the Carlsberg Laboratories, Copenhagen, Denmark, and the University of Rochester, Rochester, N. Y. In June, 1952, he was awarded the honorary degree of Doctor of Science by Simpson College, Indianola, Iowa, where he earned his undergraduate degree in 1921. He attained his doctorate at Yale in 1926.

Books

From the Workshop of Discoveries. By Otto Loewi. Price, $2.00. Pp. 62. University of Kansas Press, Lawrence, Kansas, 1953.

Delightful semipopular essays by a great scientist dealing with a variety of topics including his own important discoveries. The material was given as the Porter Lectures, Series 19. As one reads one regrets not having heard the author actually deliver these interesting and stimulating talks.

Physiological Foundations of Neurology and Psychiatry. By Ernst Gellhorn, M.D. Price, $8.50. Pp. 556. University of Minnesota Press, Minneapolis 14, 1953.

Dr. Gellhorn's work over a period of more than 30 years has been a major contribution to the delineation of some of the parameters of neurophysiologic function. In this volume of 20 chapters, the author attempts to summarize a part of the enormous experimental data which have accumulated and are particularly relevant to the clinical workers in the fields of neurology and psychiatry. Dr. Gellhorn has drawn heavily upon the work of his own laboratories over the years. His many and varied interests in neurophysiology are the warp on which he weaves the more significant experimental evidence to substantiate the dependence of function upon the ordered activity of neural structures.

The book is composed of six rather distinct parts: the subjects, the mood in which they are treated, as well as the derivative implications have a more distinct clinical flavor than is true of most neurophysiologic treatises. Then too, for the clinician there is a welcome leaven of germane applications to the substantial substrate of academic minutiae. The result is an interesting series of essays on applied neurophysiology.

The gamut includes a survey of the intrinsic and extrinsic factors which regulate neuronal activity. While the treatment is condensed necessarily, it does point up some of the molar aspects of neuronal dependence upon the components of the internal environment. Part II is a review of some contributions to the physiology and pathology of movements. The discussion includes a résumé of the motor cortical aspects, the restitution of movements after central lesions, electromyography, and material relating to experimental convulsions.

The physiology and pathology of consciousness are presented in Part III, a 47-page essay. Sixty pages are devoted to certain phases of the physiology of the autonomic system. Part V, entitled "Integrations," is the longest essay (138 pages), and treats of such phenomena as the principles of neuroendocrine action, the physiologic basis of emotion, factors involved in conditions, and homeostasis. Part VI is called "Applications"; it discusses some of the work which shows the autonomic disturbances in schizophrenia, Funkenstein's observations, and the physiologic foundation of carbon dioxide therapy.

While this book is a worth-while compilation of some experimental aspects of behavior, it must be noted that the use of such terms as "foundation" and "basis" in discussing psychologic behavior is somewhat of an overstatement. This is particularly true of the references to the psychoses in which the variations from normal in physiologic responsivity are assumed to be

causal. Sir Charles Sherrington's observation about the mind-brain problem still holds: "Physiology has not enough to offer about the brain in relation to the mind to lend the psychiatrist much help."

The Conception of Disease: Its History, Its Versions, and Its Nature. By Walther Riese, M.D. Price, $3.75. Pp. 120. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1953.

A brief philosophical excursion as to the conception of disease. The reviewer, who has always had difficulty in understanding technical philosophical writing, is not quite clear with this book as to all the author means. For example (p. 94), "The only teleological conception of disease standing the test of critical reasoning is that of an inner teleological or quasipurposeful arrangement and organization of its constituents, i. e., its symptoms."

Dermatology; Essentials of Diagnosis and Treatment. By Marion B. Sulzberger, M.D., professor and chairman, department of dermatology and syphilology, New York University Post-Graduate Medical School; director of dermatology and syphilology, Skin and Cancer Unit and University Hospital, New York University-Bellevue Medical Center, and Jack Wolf, M.D., associate professor of clinical dermatology and syphilology, New York University Post-Graduate Medical School; attending dermatologist and syphilologist, Skin and Cancer Unit and University Hospital, New York University-Bellevue Medical Center. Price, $10.00. Pp. 592, with 65 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1952.

This volume is a revision and expansion of "Dermatologic Therapy," by the same authors. It is not a dermatologic text in the true sense of the word, but a compendium on skin diseases, with emphasis on the principles of diagnosis and particularly on treatment. There are no chapters on the anatomy or physiology of the skin, none on histology or pathology, and there is no bibliography.

Almost half of the volume is devoted to the commoner skin diseases, particularly the eczema and acne group, fungous infections and pyodermas. A good deal of the material is a condensation of lectures and chapters from previous publications by the same authors. There are numerous good black-and-white illustrations and eight colored plates reprinted from *Ciba Symposia*.

If there is any drawback to the volume, it lies in its verbosity. Several of the chapters could be condensed, particularly those dealing with measures devoted to the allergic control of patients with atopic dermatitis and the chapter on urticaria, which occupies 35 pages. Also, many of the recommendations for treatment are carried over from a former day and could well be eliminated because they are obsolete. One might question, for example, such recommendations as large doses of vitamin A for the treatment of leucopenia, or chloramphenicol in rosacea, or the need for detailed directions for malaria therapy in neurosyphilis. The two chapters at the end of the book, dealing with the principles of diagnosis and treatment of syphilis, are well done.

The book is an excellent summary and guide for those with some basic training in dermatology.

Hormonal and Neurogenic Cardiovascular Disorders: Endocrine and Neuro-Endocrine Factors in Pathogenesis and Treatment. By Wilhelm Raab, M.D. Price, $15.00. Pp. 750, with 87 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1953.

The frontispiece to this book is an effective ink sketch by the author illustrating an apt quotation from Shakespeare's "Macbeth." It shows three heavy weights tugging at the heart —thyroid, catecholamines, and mineralocorticoids. The author's professed aim is to crusade for the idea that neuroendocrine and endocrine influences play a fundamental role in the origin and treatment of cardiovascular disorders. That he means business is documented by 3,726 references. The book contains the mass of evidence in a heavy style, of unduly long sentences, unrelieved by the "skill and sparkle" promised in the publisher's blurb.

As to the contents, they suffice for several crusades for the basic idea. The first part deals with experimental cardiovascular effects of hormones and neurohormones. It is a thorough review of the complex interrelations between circulatory hormones, electrolytes, myocardial and vascular function, and cardiovascular morphology. The thesis is well supported that the sodium concentration in the muscle cells of the circulatory system determines their maximal contractile power to adequate stimuli. The concentration of sodium is in turn regulated by adrenal hormones. An excellent synopsis summarizes the fact and hypotheses.

The second part of the book is dedicated to the cardiovascular aspects of endocrine and neuroendocrine syndromes. These include all the diseases characterized by hyperfunction or hypofunction of the various endocrine glands. It is very questionable whether any useful scientific or literary purpose is served by rehashing the symptoms, diagnosis, and treatment of these diseases in a discussion supposedly devoted to their cardiovascular features. The net result is a diffuse melange in which the worthwhile contribution of the author is lost in a maze of dull text-book description.

The hypertension of adrenal syndromes is ascribed to exaggerated cardiovascular muscle contraction due to varying combinations of increased intracellular sodium (mineralocorticoid effect) and the membrane depolarizing effect of the catecholamines, epinephrine, or arterenol (nor-epinephrine). The cardiovascular manifestations of hyperthyroidism are attributed to the potentiation of the catecholamines by thyroid hormone. Similarly, the cardiovascular complications in pregnancy result from a hormonally induced chemical and electrophysical burden upon the cardiovascular muscle cells.

The third part of the volume covers the endocrine and neuroendocrine factors in cardiovascular syndromes—arteriosclerosis, hypertension, shock, angina pectoris, myocardial necrosis, uremia, thiamine deficiency, congestive heart failure, etc. This section emphasizes and reemphasizes the author's credo: 1. Epinephrine and arterenol are potent metabolic agents that cause wasteful oxygen consumption by the myocardium and, ultimately, myocardial hypoxia and angina pectoris unless properly antagonized by vagal neurosecretion. 2. Thyroid hormone intensifies the metabolic and dynamic effects of the sympathomimetic amines. 3. The adrenal mineralocorticoids are injurious to cardiovascular tissue unless properly balanced by glucocorticoids. The former also determine the pressor action of catecholamines by their effect on electrolyte distribution in body fluids and on the membrane potential of contractile cells. 4. Cardiac hypertrophy and failure may result directly from hormonal metabolic effects upon the myocardium independent of mechanical work against increased peripheral resistance.

Congestive heart failure is not directly related to the sympathomimetic catecholamines except when associated with hypertension, beriberi, or uremia. However, the metabolic oxygen wastage of the myocardium corresponds to an unbalanced catecholamine effect. The general and myocardial electrolyte imbalance is attributed in large part to increased adrenal mineralocorticoids. The latter is considered a causal factor in heart failure. The role of the sympathetic system and its hormones in the induction of acute pulmonary edema is stressed. Treatment by sympathectomy, thyroidectomy, or inactivation of the thyroid by and adrenalectomy thus has a physiological basis.

The synopsis of this third section is full of question marks indicating the admittedly speculative nature of the interpretations based on inadequate evidence. These honest doubts are not so clearly indicated in the many pages of preceding text.

For his strong views, the author "expects to be branded as a hormonomaniac." His heavy reliance upon rather nonspecific methods for quantitation of catecholamines in body fluids and tissues weakens the foundations of his universal thesis. However, he presents much vasoendocrine food for thought, particularly in his discussion of the pathogenesis of "essential" hypertension and the therapeutic response to dietary sodium restriction. His enthusiasm for x-ray irradiation of the adrenals and other methods of treatment for angina pectoris is not surprising in view of the power of his faith in the logic of his theory. But a well-controlled study is still lacking to establish the basic assumption on which the logical structure is reared. The author is certainly not at his best in evaluating therapeutic results.

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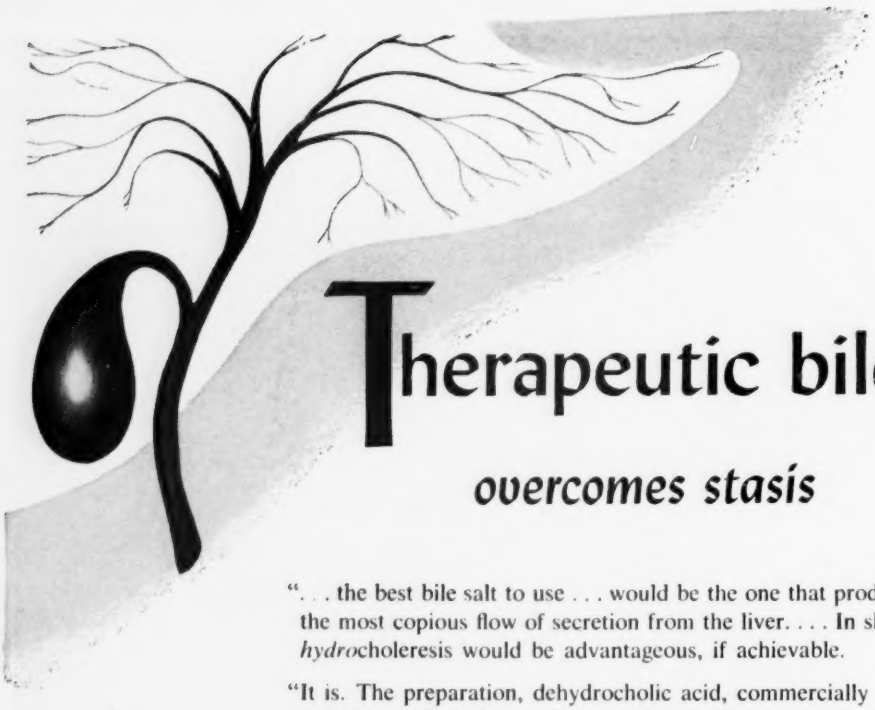

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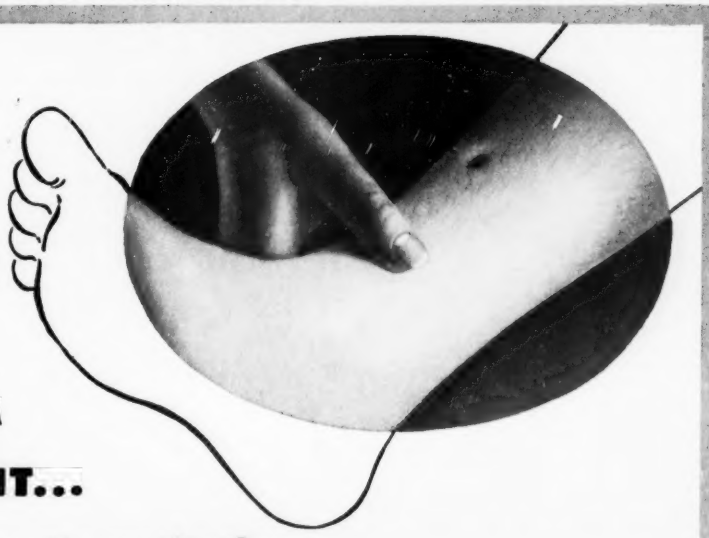

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